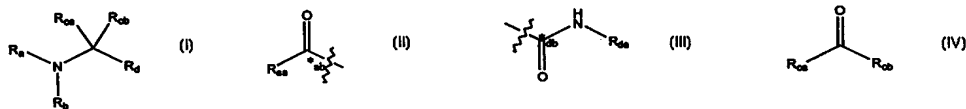




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 205/00, 205/08, 243/12, 243/24, 241/04, 241/36, 231/00, 233/22, 207/00, 207/12, 401/00, 403/00, 405/00, C07C 261/02</p>	A1	<p>(11) International Publication Number: WO 99/38844</p> <p>(43) International Publication Date: 5 August 1999 (05.08.99)</p>																																						
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/US99/01923</p> <p>(22) International Filing Date: 29 January 1999 (29.01.99)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">60/073,007</td> <td style="width: 30%;">29 January 1998 (29.01.98)</td> <td style="width: 40%;">US</td> </tr> <tr> <td>60/098,404</td> <td>31 August 1998 (31.08.98)</td> <td>US</td> </tr> <tr> <td>60/098,708</td> <td>1 September 1998 (01.09.98)</td> <td>US</td> </tr> <tr> <td>60/101,056</td> <td>18 September 1998 (18.09.98)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">US</td> <td style="width: 30%;">60/098,404 (CIP)</td> <td style="width: 40%;"></td> </tr> <tr> <td>Filed on</td> <td>31 August 1998 (31.08.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/098,708 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>1 September 1998 (01.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/101,056 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>18 September 1998 (18.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/073,007 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>29 January 1998 (29.01.98)</td> <td></td> </tr> </table> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(71) Applicant (for all designated States except US): RHONE-POULENC RORER PHARMACEUTICALS INC. [US/US]; Legal/Patents, 500 Arcola Road, Mail Stop #3C43, Collegeville, PA 19426-0997 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HULME, Christopher [GB/US]; 970 Township Line Road, Phoenixville, PA 19460 (US). MORTON, George, C. [US/US]; 313 Ross Lane, Collegeville, PA 19426 (US). SALVINO, Joseph, M. [US/US]; 272 Second Street, Schwenksville, PA 19473 (US). LABAUDINIÈRE, Richard, F. [FR/US]; 220 Richard Way, Collegeville, PA 19426 (US). MASON, Helen, J. [GB/US]; 4 Eagle Creek Court, Skillman, NJ 08558 (US). MORRISSETTE, Matthew, M. [US/US]; 1922 Linda Lane, Pottstown, PA 19464 (US). MA, Liang [CN/US]; 251 West Dekalb Pike, E214, King of Prussia, PA 19406 (US). CHERRIER, Marie-Pierre [FR/US]; The Village of Pickering Run C-5, 800 Kimberton Road, Phoenixville, PA 19460 (US).</p> <p>(74) Agent: NEWMAN, Irving; Rhône-Poulenc Rorer Pharmaceuticals Inc., 500 Arcola Road, P.O. Box 5093, Collegeville, PA 19426-0997 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/US99/01923</p> <p>(22) International Filing Date: 29 January 1999 (29.01.99)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">60/073,007</td> <td style="width: 30%;">29 January 1998 (29.01.98)</td> <td style="width: 40%;">US</td> </tr> <tr> <td>60/098,404</td> <td>31 August 1998 (31.08.98)</td> <td>US</td> </tr> <tr> <td>60/098,708</td> <td>1 September 1998 (01.09.98)</td> <td>US</td> </tr> <tr> <td>60/101,056</td> <td>18 September 1998 (18.09.98)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">US</td> <td style="width: 30%;">60/098,404 (CIP)</td> <td style="width: 40%;"></td> </tr> <tr> <td>Filed on</td> <td>31 August 1998 (31.08.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/098,708 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>1 September 1998 (01.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/101,056 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>18 September 1998 (18.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/073,007 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>29 January 1998 (29.01.98)</td> <td></td> </tr> </table>	60/073,007	29 January 1998 (29.01.98)	US	60/098,404	31 August 1998 (31.08.98)	US	60/098,708	1 September 1998 (01.09.98)	US	60/101,056	18 September 1998 (18.09.98)	US	US	60/098,404 (CIP)		Filed on	31 August 1998 (31.08.98)		US	60/098,708 (CIP)		Filed on	1 September 1998 (01.09.98)		US	60/101,056 (CIP)		Filed on	18 September 1998 (18.09.98)		US	60/073,007 (CIP)		Filed on	29 January 1998 (29.01.98)		<p>(71) Applicant (for all designated States except US): RHONE-POULENC RORER PHARMACEUTICALS INC. [US/US]; Legal/Patents, 500 Arcola Road, Mail Stop #3C43, Collegeville, PA 19426-0997 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HULME, Christopher [GB/US]; 970 Township Line Road, Phoenixville, PA 19460 (US). MORTON, George, C. [US/US]; 313 Ross Lane, Collegeville, PA 19426 (US). SALVINO, Joseph, M. [US/US]; 272 Second Street, Schwenksville, PA 19473 (US). LABAUDINIÈRE, Richard, F. [FR/US]; 220 Richard Way, Collegeville, PA 19426 (US). MASON, Helen, J. [GB/US]; 4 Eagle Creek Court, Skillman, NJ 08558 (US). MORRISSETTE, Matthew, M. [US/US]; 1922 Linda Lane, Pottstown, PA 19464 (US). MA, Liang [CN/US]; 251 West Dekalb Pike, E214, King of Prussia, PA 19406 (US). CHERRIER, Marie-Pierre [FR/US]; The Village of Pickering Run C-5, 800 Kimberton Road, Phoenixville, PA 19460 (US).</p> <p>(74) Agent: NEWMAN, Irving; Rhône-Poulenc Rorer Pharmaceuticals Inc., 500 Arcola Road, P.O. Box 5093, Collegeville, PA 19426-0997 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(21) International Application Number: PCT/US99/01923</p> <p>(22) International Filing Date: 29 January 1999 (29.01.99)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">60/073,007</td> <td style="width: 30%;">29 January 1998 (29.01.98)</td> <td style="width: 40%;">US</td> </tr> <tr> <td>60/098,404</td> <td>31 August 1998 (31.08.98)</td> <td>US</td> </tr> <tr> <td>60/098,708</td> <td>1 September 1998 (01.09.98)</td> <td>US</td> </tr> <tr> <td>60/101,056</td> <td>18 September 1998 (18.09.98)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">US</td> <td style="width: 30%;">60/098,404 (CIP)</td> <td style="width: 40%;"></td> </tr> <tr> <td>Filed on</td> <td>31 August 1998 (31.08.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/098,708 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>1 September 1998 (01.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/101,056 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>18 September 1998 (18.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/073,007 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>29 January 1998 (29.01.98)</td> <td></td> </tr> </table>	60/073,007	29 January 1998 (29.01.98)	US	60/098,404	31 August 1998 (31.08.98)	US	60/098,708	1 September 1998 (01.09.98)	US	60/101,056	18 September 1998 (18.09.98)	US	US	60/098,404 (CIP)		Filed on	31 August 1998 (31.08.98)		US	60/098,708 (CIP)		Filed on	1 September 1998 (01.09.98)		US	60/101,056 (CIP)		Filed on	18 September 1998 (18.09.98)		US	60/073,007 (CIP)		Filed on	29 January 1998 (29.01.98)		<p>(71) Applicant (for all designated States except US): RHONE-POULENC RORER PHARMACEUTICALS INC. [US/US]; Legal/Patents, 500 Arcola Road, Mail Stop #3C43, Collegeville, PA 19426-0997 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HULME, Christopher [GB/US]; 970 Township Line Road, Phoenixville, PA 19460 (US). MORTON, George, C. [US/US]; 313 Ross Lane, Collegeville, PA 19426 (US). SALVINO, Joseph, M. [US/US]; 272 Second Street, Schwenksville, PA 19473 (US). LABAUDINIÈRE, Richard, F. [FR/US]; 220 Richard Way, Collegeville, PA 19426 (US). MASON, Helen, J. [GB/US]; 4 Eagle Creek Court, Skillman, NJ 08558 (US). MORRISSETTE, Matthew, M. [US/US]; 1922 Linda Lane, Pottstown, PA 19464 (US). MA, Liang [CN/US]; 251 West Dekalb Pike, E214, King of Prussia, PA 19406 (US). CHERRIER, Marie-Pierre [FR/US]; The Village of Pickering Run C-5, 800 Kimberton Road, Phoenixville, PA 19460 (US).</p> <p>(74) Agent: NEWMAN, Irving; Rhône-Poulenc Rorer Pharmaceuticals Inc., 500 Arcola Road, P.O. Box 5093, Collegeville, PA 19426-0997 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>			
60/073,007	29 January 1998 (29.01.98)	US																																						
60/098,404	31 August 1998 (31.08.98)	US																																						
60/098,708	1 September 1998 (01.09.98)	US																																						
60/101,056	18 September 1998 (18.09.98)	US																																						
US	60/098,404 (CIP)																																							
Filed on	31 August 1998 (31.08.98)																																							
US	60/098,708 (CIP)																																							
Filed on	1 September 1998 (01.09.98)																																							
US	60/101,056 (CIP)																																							
Filed on	18 September 1998 (18.09.98)																																							
US	60/073,007 (CIP)																																							
Filed on	29 January 1998 (29.01.98)																																							

(54) Title: METHOD FOR PREPARING AN N-[(ALIPHATIC OR AROMATIC)CARBONYL]-2-AMINOACETAMIDE COMPOUND AND A CYCLYZED COMPOUND

**(57) Abstract**

The present invention relates to a method for preparing an N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound of formula (I) wherein R_a is (II); R_{aa} is hydrogen, optionally substituted aliphatic or optionally substituted aromatic; R_b is hydrogen, optionally substituted aliphatic or optionally substituted aromatic; R_{ca} and R_{cb} are independently hydrogen, optionally substituted aliphatic or optionally substituted aromatic; R_d is (III); and R_{da} is optionally substituted aliphatic or optionally substituted aromatic; and R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_b , R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or R_b is substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_{aa} , R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or R_{ca} and R_{cb} are independently substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_{aa} , R_b , R_{ca} , R_{cb}

or R_{da} where each is at least substituted with an activated carboxylic acid to form a 5–7 membered cyclic ring; or R_{da} is substituted with a primary or secondary protected amine that upon deprotection can react with at least one of R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5–7 membered cyclic ring, provided that when R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with R_b at least substituted with an activated carboxylic acid, then R_{aa} is other than substituted aliphatic, comprising reacting the following four compounds: a carbonyl compound of formula (IV), an amine compound of formula NH₂R_b, an isonitrile compound of formula NCR_{da}, and an acid compound of formula R_aCO₂H, to produce the N–[(aliphatic or aromatic)carbonyl]–2–aminoacetamide compound, and the N–[(aliphatic or aromatic)carbonyl]–2–aminoacetamide compound. The invention is also directed to a method for cyclizing N–[(aliphatic or aromatic)carbonyl]–2–aminoacetamide compound to a cyclic compound selected from the group consisting of a 1,4–benzodiazepine–2,5–dione derivative, diketopiperazine derivative, ketopiperazine derivative, lactam derivative, 1,4–benzodiazapine derivative and dihydroquinoxalinones derivative, and the cyclized compound.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

METHOD FOR PREPARING AN N-[(ALIPHATIC OR AROMATIC)CARBONYL]-2-AMINOACETAMIDE COMPOUND AND A CYCLYZED COMPOUND

This invention is directed to a method for preparing an N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound, and a cyclized compound therefrom, and the compounds.

Background of the Invention

1,4-benzodiazepine-2,5-diones are an important class of biologically active compounds. This class of compounds has been identified as having platelet aggregation inhibitor activity, anticonvulsant activity, anxiolytic activity and as anti tumor agents (Mc Dowell, R.S. et al., J. Am. Chem. Soc., 1994, 116, 5077; Cho, N.S. et al., J Heterocycl. Chem., 1989, 26, 1807; Wright, W.B. et al., J. Med. Chem., 1978, 21, 1087; Jones; G.B. et al., Anti-Cancer Drug Des. 1990, 5, 249).

Diketopiperazines are known to be ligands of neurokinin-2 receptors and neurokinin-3 receptors (Gordon, D.W.; Steele, J. Bioorg. Med. Chem. Lett., 1995, 5, 47. (b) Terrett, N.K.; Gardner, M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J., Tetrahedron, 1995, 51, 8135) and are useful in the treatment of asthma, inflammation, Parkinsons disease, anxiety, psychosis, epilepsy and pain.

Reports of the biological utility of ketopiperazines have appeared in several areas, including applications as antagonists of the platelet glycoprotein IIb-IIIa (Takada, S.; Kurokawa, T.; Miyazaki, K.; Iwasa, S.; Ogawa, Y. Pharm. Res. 1997, 14, 1146), and substance P (Wright, H. B.; Martin, D. L. J. Med. Chem.. 1968, 11, 390) and as hypocholesteremic agents (Piercey, M. F. ; Moon, M. W.; Blinn, J. R. Brain Res., 1986, 385, 74).

Reports of the biological utility of dihydroquinoxalinones (also known as benzopiperazinones) have appeared in several areas, including applications as inhibitors of aldose reductase (Sarges, R.; Lyga, J.W. J. Heterocycl. Chem. 1988, 25, 1474), partial agonists of the γ -aminobutyric acid (GABA)/benzodiazepine receptor complex (Tenbrink, R.E.; Im, W.B.; Sethy, V.H.; Tang, A.H.; Carter, D.B. J. Med. Chem. 1994, 37, 758), angiotensin II receptor antagonists (Kim, K.S.; Qian, L.; Bird, J.E.; Dickinson, K.E.; Moreland, S.; Schaeffer, T.R.; Waldron, T.L.; Delaney, C.L.; Weller, H.N.; Miller, A.V. J. Med. Chem. 1993, 36, 2335) and are known to possess antiviral activity as associated with HIV (Meichsner, C.; Riess, G.; Kleim, J.P.; Roesner, M.; Paessens, A.; Blunck, M. Eur. Pat. Appl. EP 657166 A1 950614).

Early work pioneered by Freidinger (Freidinger, R.M.; Perlow, D.S.; Veber, D.F. J. Org. Chem. 1982, 47, 104) showed γ -lactams to be a useful new type of conformational constraint in peptides and useful in the synthesis of LHRH (Samenen, J.; Hempel, J.C.; Narindray, D.; Regoli, D. 'Peptides.

Chemistry and Biology', Proc. 10th Am. Peptide Symp. 1988, 137), angiotensin II (Douglas, A.J.; Mulholland, G.; Walker, B.; Guthrie, D.J.S.; Elmore, D.T.; Murphy, R.F. Biochem. Soc. Trans. 1988, 16, 175), pentagastrin (Piercey, M.F.; Moon, M.W.; Blinn, J.R.; Dobry-Schreur, P.J.K. Brain Res. 1986, 385, 74), and substance P analogues. The lactams described herein, in particular those produced via
5 cyclization of a primary amine, result in potential ATP competitive kinase inhibitors possessing functionality that may mimic the N1 - N6 interaction of ATP binding to a relevant kinase (Myers, M. R.; He, W.; Hulme, C. Curr. Pharm. Design. 1997, 3, 473).

Benzodiazepines have been shown to have utility as GPIIb/IIIa receptor antagonists (Ku, T. W.; Miller, W. H.; Bondinell, W. E.; Erhard, K. F.; Keenan, R. M.; Nichols, A. J.; Peishoff, C. E.; Samenen, J. M.; Wong, A. S.; Huffman, W. F. J. Med. Chem. 1995, 38, 9 - 12) and may be useful for the
10 treatment of acute myocardial infarction, unstable angina, or thrombotic stroke. Recent developments have extended the therapeutic utility of this class of molecule to include integrin antagonists (for example antagonists of the vitronectin receptor), useful for the stimulation of bone formation and
15 treatment of bone fractures, osteoporosis and other bone-related disorders (Drake, F.H. WO98115278-A1, 1997).

Dihydroimidazoles (or imidazolines) have been shown to have biological utility as anti-depressants and additionally imidazoline receptors are widely distributed in both the peripheral and
20 central nervous system playing potential roles in the regulation of several physiological effects (Pigini, M.; Bousquet, P.; Carotti, A.; Dontenwill, M.; Gianella, M.; Moriconi, R.; Piergentili, A.; Quaglia, W.; Tayebati, S.K.; Brasili, L.; Bioorg. Med. Chem. 1997, 5, 833; Harfenist, M.; Heuser, D.J.; Joyner, C.T.; Batchelor, J.F.; White, H.L.; J. Med. Chem. 1996, 39, 1857; Jackson, H.C.; Griffin, I.J.; Nutt, D.J.; Br. J. Pharmacol. 1991, 104, 258; and Tibirica, E.; Feldman, J.; Mermet, C.; Gonon, F.; Bousquet, P. J.
25 Pharmacol. 1987, 134, 1). The imidazoline moiety has also been extensively studied as an amide bond replacement in biologically active peptides (Gilbert, I.; Rees, D.C.; Richardson, R.S. Tetrahedron Lett. 1991, 32, 2277; and Jones, R.C.F.; Ward, G.J. Tetrahedron Lett. 1988, 29, 3853).

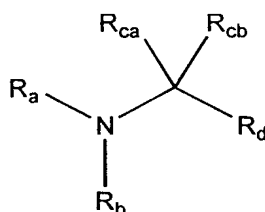
Pressures on the pharmaceutical industry have increased significantly to meet the economic
30 challenges of the 1990s. As a consequence, efforts in both industrial and academic sectors are now being directed at new technologies for attacking drug discovery in a more efficient and cost-effective manner. As such, with the recent development of combinatorial chemistry and high speed parallel synthesis within the Lead Discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest. From a practical consideration one-pot reactions, such as the Ugi and Passerini reactions, are
35 easily automated and production of diverse or directed libraries of small organic molecules is thus both facile and high-throughput. Despite this tremendous synthetic potential, the Ugi reaction is limited by producing products that are flexible and peptidic-like, often being classified as 'non-drug-like' and suffering from bioavailability problems. Interestingly several novel intramolecular derivatives of this

3

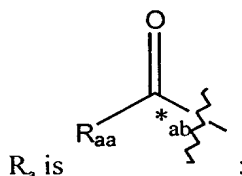
versatile reaction have recently been reported where constrained products are achieved by intercepting the intermediate nitrilium ion of the Ugi reaction. An alternative approach and the one described in this application is to constrain the Ugi product via a so-called secondary reaction after initial formation of the classical Ugi product. Production of the derivatives described herein is facile and amenable to automated high throughput production, allowing production of vast arrays of biologically relevant molecules (in the range of at least 10,000 molecules/template revealed in good purity).

Summary of the Invention

The present invention relates to a method for preparing an N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound of the formula



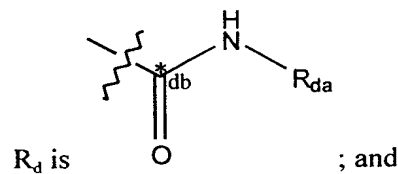
wherein



R_{aa} is hydrogen, optionally substituted aliphatic or optionally substituted aromatic;

R_b is hydrogen, optionally substituted aliphatic or optionally substituted aromatic;

R_{ca} and R_{cb} are independently hydrogen, optionally substituted aliphatic or optionally substituted aromatic;



R_{da} is optionally substituted aliphatic or optionally substituted aromatic; and

4

R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_b , R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

5

R_b is substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_{aa} , R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

- 10 R_{ca} and R_{cb} are independently substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_{aa} , R_b , R_{ca} , R_{cb} or R_{da} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

- 15 R_{da} is substituted with a primary or secondary protected amine that upon deprotection can react with at least one of R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring,

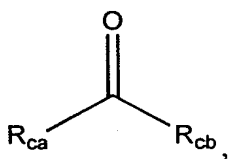
- 20 provided that when R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with R_b at least substituted with an activated carboxylic acid, then R_{aa} is other than substituted aliphatic,

comprising

reacting the following four compounds:

25

an carbonyl compound of formula



- 30 an amine compound of formula

NH_2R_b ,

an isonitrile compound of formula

35

5

NCR_{da}, and

an acid compound of formula

5 R_aCO₂H,

to produce the N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound, and the N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound. The invention is also directed to a method for cyclizing N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound to a cyclic compound
10 selected from the group consisting of a 1,4-benzodiazepine-2,5-dione derivative, diketopiperazine derivative, ketopiperazine derivative, lactam derivative, 1,4-benzodiazapine derivative and dihydroquinoxalinones derivative, and the cyclized compound.

DETAILED DESCRIPTION

15

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Acid bioisostere" means a group which has chemical and physical similarities producing
20 broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, 1986, 21, p.283 "Bioisosterism In Drug Design"; Yun, Hwahak Sekye, 1993, 33, p.576-579 "Application Of Bioisosterism To New Drug Design"; Zhao, Huaxue Tongbao, 1995, p.34-38 "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design"; Graham, Theochem, 1995, 343, p.105-109 "Theoretical Studies Applied To Drug Design:ab initio Electronic
25 Distributions In Bioisosteres"). Examples of suitable acid bioisosteres include: -C(=O)-NHOH, -C(=O)-CH₂OH, -C(=O)-CH₂SH, -C(=O)-NH-CN, sulfo, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, heteroarylsulphonylcarbamoyl, N-methoxycarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or heterocyclic phenols such as 3-hydroxyisoxazolyl and 3-hydroxy-1-methylpyrazolyl.

30

"Acidic functional group" means a group with an acidic hydrogen within it. The "corresponding protected derivatives" are those where the acidic hydrogen atom has been replaced with a suitable protecting group, to block or protect the acid functionality while the reactions involving other functional sites of the compound are carried out. Such protecting groups are well known to those skilled in the art,
35 having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. For suitable protecting groups see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Exemplary acidic functional

groups include carboxyl (and acid bioisosteres), hydroxy, mercapto and imidazole. Examples of carboxylic acid protecting groups include esters such as methoxymethyl, methylthiomethyl, tetrahydropyranyl, substituted and unsubstituted phenacyl, 2,2,2-trichloroethyl, *tert*-butyl, cinnamyl, dialkylaminoalkyl (e.g., dimethylaminoethyl and the like), trimethylsilyl, and the like, and amides and hydrazides including N,N-dimethyl, 7-nitroindolyl, hydrazide, N-phenylhydrazide, C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; alkanoyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like; alkoxycarbonyloxyalkyl, such as t-butyloxycarbonyloxymethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

"Acyl" means an H-CO- or alkyl-CO- group wherein the alkyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, t-butylacetyl, butanoyl and palmitoyl.

"Aliphatic" means a radical derived from a non aromatic C-H bond by removal of the hydrogen atom. The aliphatic radical may be further substituted by additional aliphatic or aromatic radicals as defined herein. Representative aliphatic groups include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aralkenyl, aralkyloxyalkyl, aralkyloxycarbonylalkyl, aralkyl, aralkynyl, aralkyloxyalkenyl, heteroaralkenyl, heteroaralkyl, heteroaralkyloxyalkenyl, heteroaralkyloxyalkyl, heteroaralkynyl, fused arylcycloalkyl, fused heteroaryl cycloalkyl, fused arylcycloalkenyl, fused heteroaryl cycloalkenyl, fused arylheterocyclyl, fused heteroaryl heterocyclyl, fused arylheterocyclenyl, fused heteroaryl heterocyclenyl, and the like as described herein, which are optionally substituted including to a solid support (resin) directly or through a linker attached to the to the solid support. including to a solid, "Aliphatic", as used herein, also encompasses the residual, non-carboxyl portion of natural and unnatural amino acids as defined herein.

"Aromatic" means a radical derived from an aromatic C-H bond by removal of the hydrogen atom. Aromatic includes both aryl and heteroaryl rings as defined herein. The aryl or heteroaryl ring may be further substituted by additional aliphatic or aromatic radicals as defined herein. Representative aromatic groups include aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused

heterocyclenylheteroaryl, fused heterocyclylheteroaryl, and the like, as described herein, which are optionally substituted including to a solid support (resin) directly or through a linker attached to the to the solid support.

5 "Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkenoyl" means an alkenyl-CO- group wherein alkenyl is as defined herein.

10 "Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 5 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted with one or more
15 "alkenyl group substituents" which may be the same or different, and include halo, alkenyloxy, cycloalkyl, cyano, hydroxy, alkoxy, carboxy, alkynyloxy, aralkoxy, aryloxy, aryloxycarbonyl, alkylthio, heteroaralkyloxy, heterocyclyl, heterocyclylalkyloxy, alkoxycarbonyl, aralkoxycarbonyl, heteroaralkyloxycarbonyl or Y^1Y^2N- , Y^1Y^2NCO- or $Y^1Y^2NSO_2-$, wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or for where the substituent is Y^1Y^2N- , then one of Y^1 and
20 Y^2 may be acyl or aroyl as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is Y^1Y^2NCO- or $Y^1Y^2NSO_2$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered heterocyclyl or heterocyclenyl. Exemplary alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, methoxyethyl, carboxymethyl,
25 methoxycarbonyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl.

"Alkenyloxy" means an alkenyl-O- group wherein the alkenyl group is as herein described.
30 Exemplary alkenyloxy groups include allyloxy and 3-butenyloxy.

"Alkenyloxyalkyl" means alkenyl-O-alkyl group wherein the alkyl and alkenyl groups are as described herein.

35 "Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Alkoxyalkyl" means an alkyl-O-alkyl- group wherein the alkyl groups are independent as herein described. Exemplary alkoxy groups include methoxyethyl, ethoxymethyl, *n*-butoxymethyl and cyclopentylmethyloxyethyl.

5 "Aminoiminomethyl" means a $\text{NH}_2\text{C}(=\text{NH})$ - group. It is known that this moiety may be mono or di-protected to afford, for example (alkoxycarbonylamino)iminomethyl and (alkoxycarbonylamino)alkoxycarbonyliminomethyl groups.

"Alkoxycarbonyl" means an alkyl-O-CO- group, wherein the alkyl group is as herein defined.
10 Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, and *t*-butoxycarbonyl.

"Alkoxycarbonylalkyl" means an alkyl-O-OC-alkyl- group wherein the alkyl groups are as herein defined. Preferred groups include methoxy- and ethoxy-carbonylmethyl and carbonyl ethyl.

15 "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl may be substituted with one or more "alkyl group substituents" which
20 may be the same or different, and include halo, alkenyloxy, cycloalkyl, aroyl, cyano, hydroxy, alkoxy, carboxy, alkynyloxy, aralkoxy, aryloxy, aryloxycarbonyl, alkylthio, heteroarylthio, aralkylthio, arylsulphonyl, alkylsulphonyl, alkylphosphonate, heteroaralkyloxy, heterocyclyl, fused heteroarylcyaloalkenyl, fused heteroarylcyaloalkyl, fused heteroarylheterocyclenyl, fused heteroarylheterocyclyl, fused arylcyaloalkenyl, fused arylcyaloalkyl, fused arylheterocyclenyl, fused
25 arylheterocyclyl, alkoxycarbonyl, aralkoxycarbonyl, (alkoxycarbonylamino)iminomethyl, (alkoxycarbonylamino)alkoxycarbonyliminomethyl, heteroaralkyloxycarbonyl or $\text{Y}^1\text{Y}^2\text{N}-$, $\text{Y}^1\text{Y}^2\text{NCO}-$ or $\text{Y}^1\text{Y}^2\text{NSO}_2-$, wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl, heteroaroyl, aralkyl or heteroaralkyl, or for where the substituent is $\text{Y}^1\text{Y}^2\text{N}-$, then one of Y^1 and Y^2 may be acyl, alkoxycarbonyl or aroyl as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent
30 is $\text{Y}^1\text{Y}^2\text{NCO}-$ or $\text{Y}^1\text{Y}^2\text{NSO}_2$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered heterocyclyl or heterocyclenyl. Exemplary alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, *n*-nonyl, decyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl. Preferred alkyl group substituents are
35 fused arylcyaloalkenyl, cyano, fused arylcyaloalkyl, aralkylthio, $\text{Y}^1\text{Y}^2\text{N}-$, $\text{Y}^1\text{Y}^2\text{NCO}-$, fused arylheterocyclenyl, fused arylheterocyclyl, hydroxy, heterocyclyl, aralkoxy, alkoxycarbonyl, alkylthio, aryloxy, aroyl, heteroaroyl, arylsulphonyl, heteroarylthio alkylphosphonate, alkylsulphonyl,

(alkoxycarbonylamino)iminomethyl, (alkoxycarbonylamino)alkoxycarbonyliminomethyl, and cycloalkyl.

"Alkylcarbamoyl" is an alkyl-NH-CO- group wherein the alkyl group is herein defined.

"Alkylphosphonate" means an (alkylO)₂P=O- group wherein the alkyl groups are independent of each other are herein defined.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above.

Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO₂- group wherein the alkyl group is as defined above.

Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulphonylcarbamoyl" means an alkyl-SO₂-NH-C(=O)- group wherein the alkyl group is as herein described. Preferred alkylsulphonylcarbamoyl groups are those wherein the alkyl group is C₁₋₄ alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as herein described. Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkynyl group may be substituted with one or more "alkynyl group substituents" which may be the same or different, and include halo, alkenyloxy, cycloalkyl, cyano, hydroxy, alkoxy, carboxy, alkynyloxy, aralkoxy, aryloxy, aryloxy carbonyl, alkylthio, heteroaralkyloxy, heterocyclyl, heterocyclylalkyloxy, alkoxycarbonyl, aralkoxycarbonyl, heteroaralkyloxycarbonyl or Y¹Y²N-, Y¹Y²NCO- or Y¹Y²NSO₂-, wherein Y¹ and Y² are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl or aroyl as defined herein and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NCO- or Y¹Y²NSO₂, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered heterocyclyl or heterocyclenyl. Exemplary alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, pyridylmethyloxycarbonylmethyl. Exemplary

alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.

“Alkynyloxy” means an alkynyl-O- group wherein the alkynyl group is as herein described.

5 Exemplary alkynyloxy groups include propynyloxy and 3-butyloxy.

“Amino acid” means an amino acid selected from the group consisting of natural and unnatural amino acids as defined herein. Preferred amino acids are those possessing an α -amino group. The amino acids may be neutral, positive or negative depending on the substituents in the side chain.

10 “Neutral amino acid” means an amino acid containing uncharged side chain substituents. Exemplary neutral amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine and cysteine. “Positive amino acid” means an amino acid in which the side chain substituents are positively charged at physiological pH. Exemplary positive amino acids include lysine, arginine and histidine. “Negative amino acid” means an amino acid in which the side
15 chain substituents bear a net negative charge at physiological pH. Exemplary negative amino acids include aspartic acid and glutamic acid. Preferred amino acids are α -amino acids. Exemplary natural amino acids are isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid and glutamic acid.

20 “Unnatural amino acid” means an amino acid for which there is no nucleic acid codon. Examples of unnatural amino acids include, for example, the D-isomers of the natural α -amino acids as indicated above; Aib (aminobutyric acid), β Aib (3-aminoisobutyric acid), Nva (norvaline), β -Ala, Aad (2-aminoadipic acid), β Aad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ -aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminobutyric acid), α -aminopimelic acid, TMSA
25 (trimethylsilyl-Ala), aIle (allo-isoleucine), Nle (norleucine), *tert*-Leu, Cit (citrulline), Orn, Dpm (2,2'-diaminopimelic acid), Dpr (2,3-diaminopropionic acid), α - or β -Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), and the like; cyclic amino acids; N- α -alkylated amino acids such as MeGly (N- α -methylglycine), EtGly (N- α -ethylglycine) and EtAsn (N- α -ethylasparagine); and amino acids in which the α -carbon bears two side-chain substituents. The names of natural and unnatural amino
30 acids and residues thereof used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in "Nomenclature of α -Amino Acids (Recommendations, 1974)" Biochemistry, 14(2), (1975). To the extent that the names and abbreviations of amino acids and residues thereof employed in this specification and appended claims differ from those noted, differing names and
35 abbreviations will be made clear.

“Amino acid side chains” means the substituent found on the carbon between the amino and carboxy groups in α -amino acids. For examples of “corresponding protected derivatives” of amino acid

side chains, see T.W. Green and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

"Amine protecting group" means an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, cf, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred amine protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethylpropynyloxycarbonyl, benzyloxycarbonyl (CBZ), *p*-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, and the like.

"Acid labile amine protecting group" means an amine protecting group as defined above which is readily removed by treatment with acid while remaining relatively stable to other reagents. Preferred acid labile amine protecting groups include *tert*-butoxycarbonyl (BOC), 2-(4-biphenyl)-isopropoxy carbonyl.

"Base labile amine protecting group" means an amine protecting group as defined above which is readily removed by treatment with base while remaining relatively stable to other reagents. Preferred base labile amine protecting groups include 9-fluorenylmethoxycarbonyl (FMOC).

"Hydrogenation labile amine protecting group" means an amine protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile amine protecting group is benzyloxycarbonyl (CBZ).

"Hydrogenation labile acid protecting group" means an acid protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile acid protecting group is benzyl.

"Analogue" means a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the pharmaceutical and/or pharmacological activities characteristic of said compound or class.

"Aralkenyl" means an aryl-alkenyl- group wherein the aryl and alkenyl are as herein described. Preferred aralkenyls contain a lower alkenyl moiety. An exemplary aralkenyl group is 2-phenethenyl.

5 "Aralkoxy" means an aralkyl-O- group wherein the aralkyl groups is as herein described. Exemplary aralkoxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Aralkoxyalkyl" means an aralkyl-O-alkyl group wherein the aralkyl and alkyl groups are as herein described. An exemplary aralkoxyalkyl group is benzyloxyethyl.

10 "Aralkoxycarbonyl" means an aralkyl-O-CO- group wherein the aralkyl groups is as herein described. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

15 "Aralkoxycarbonylalkyl" means an aralkyl-OOC-alkyl- group wherein the alkyl and aralkyl groups are as herein described. Preferred groups include benzyloxy- methyl and ethyl.

"Aralkyl" means an alkyl group substituted by one or more aryl groups, wherein the aryl and alkyl are as herein described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2,2-diphenylethyl, 2,2-diphenylmethyl, 2-phenethyl and naphthalenemethyl.

20 "Aralkylamino" means an aryl-alkyl-NH- group wherein aryl and alkyl are as defined herein.

"Aralkyloxyalkenyl" means an aralkyl-O-alkenyl group wherein the aralkyl and alkenyl groups are as herein described. An exemplary aralkyloxyalkenyl group is 3-benzyloxyallyl.

25 "Aralkylsulfonyl" means an aralkyl-SO₂- group wherein the aralkyl group is as herein described.

"Aralkylsulfinyl" means an aralkyl-SO- group wherein the aralkyl group is as herein described.

30 "Aralkylthio" means an aralkyl-S- group wherein the aralkyl group is as herein described. An exemplary aralkylthio group is benzylthio.

"Aroyl" means an aryl-CO- group wherein the aryl group is as herein described. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

35 "Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. The aryl is optionally substituted with one or

more "ring system substituents" which may be the same or different, and are as defined herein. Representative aryl groups include phenyl or naphthyl, or phenyl substituted or naphthyl substituted groups. Preferred aryl groups are phenyl or naphthyl.

5 "Aralkenyl" means an aryl-alkenyl- group wherein the aryl and alkenyl moiety are as described herein. Preferred alkenyl groups contain a C₂₋₁₂ alkenyl moiety. Exemplary arylalkenyl groups include styryl, 4-phenyl-1,3-pentadienyl, 2,5-dimethyl-2-phenyl-4-hexenyl,

10 "Aralkynyl" means an aryl-alkynyl- group wherein the aryl and alkynyl moiety are as described herein. Exemplary arylalkynyl groups include phenylacetylene and 3-phenylbut-2-ynyl.

"Aryldiazo" means an aryl-azo- group wherein the aryl and azo groups are as defined herein.

15 "Arylcarbamoyl" is an aryl-NHCO- group, wherein the aryl group is as defined herein.

20 "Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl as defined herein. Preferred fused arylcycloalkenyls are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The fused arylcycloalkenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. Representative fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like.

25 "Fused arylcycloalkyl" means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. The fused arylcycloalkyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. Representative fused arylcycloalkyl includes 1,2,3,4-tetrahydronaphthyl, 5,6,7,8-tetrahydronaphth-1-yl, and the like. Preferred
30 fused arylcycloalkyl include indanyl,

35 "Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl as defined herein. Preferred fused arylheterocyclenyls are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclenyl portion of the fused arylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused arylheterocyclenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The

nitrogen atom of a fused arylheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused arylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused arylheterocyclenyl include 3H-indoliny, 1H-2-oxoquinoly, 2H-1-oxoisoquinoly, 1,2-dihydroquinoliny, 3,4-dihydroquinoliny,
5 indazolyl, 1,2-dihydroisoquinoliny, benzotriazolyl, 3,4-dihydroisoquinoliny, and the like.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclyl
10 portion of the fused arylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused arylheterocyclyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused arylheteroaryl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl
15 portion of the fused arylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative preferred fused arylheterocycl ring systems include indoliny, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindol-2-yl, 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4-tetrahydrobenz[g]isoquinolin-2-yl, 1,3-benzodioxole, and the like.

20 "Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein. Exemplary groups include phenoxy and 2-naphthyloxy.

"Aryloxyalkyl" means an aryl-O-alkyl- group wherein the aryl or alkyl groups are as herein
25 described. An exemplary aryloxyalkyl groups is phenoxypropyl.

"Aryloxyalkenyl" means an aryl-O-alkenyl- group wherein the aryl or alkenyl groups are as herein described. An exemplary aryloxyalkenyl groups is phenoxyallyl.

30 "Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined herein. Exemplary aryloxycarbonyl groups include phenoxy carbonyl and naphthoxycarbonyl.

"Aryloxycarbonylalkyl" means an aryl-O-OC-alkyl- group. Preferred groups include phenoxy carbonyl- methyl and ethyl.

35 "Arylsulfonyl" means an aryl-SO₂- group wherein the aryl group is as defined herein.

"Arylsulfinyl" means an aryl-SO- group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as herein described. Exemplary arylthio groups include phenylthio and naphthylthio.

5 "Basic nitrogen atom" means an sp^2 or sp^3 hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Examples of basic nitrogen atoms include optionally substituted imino, optionally substituted amino and optionally substituted amidino groups.

"Carbamoyl" is an NH_2-CO- group.

10 "Carboxy" means a $HO(O)C-$ (carboxylic acid) group.

"Carboxyalkyl" means an $HOOC-alkyl-$ group wherein the alkyl group is as defined herein. Preferred groups include carboxymethyl and carboxyethyl.

15 "Compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I), and compounds of formula (II), as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is
20 meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

"Cycloalkoxy" means an cycloalkyl-O- group wherein the cycloalkyl group is as herein
25 described. Exemplary cycloalkoxy groups include cyclopentyloxy and cyclohexyloxy.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The cycloalkyl is optionally substituted with one or more "ring system substituents" which may be the same
30 or different, and are as defined herein. Representative monocyclic cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, 6,6-dimethylbicyclo[3.1.1]heptane, and the like. Preferred ring system substituents for a cycloalkyl are alkyl, aralkoxy, amidino, hydroxy, or Y^1Y^2N- as defined herein.

35 "Cycloalkylcarbonyl" means a cycloalkyl-CO- group, wherein cycloalkyl is as hereinbefore defined. Exemplary cycloalkylcarbonyl groups include cyclopropylcarbonyl.

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The cycloalkenyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. A representative multicyclic cycloalkenyl is norbornylenyl. Preferred ring system substituents for a cycloalkyl are amidino or Y^1Y^2N - as defined herein

"Derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

"Diazo" means a bivalent $-N=N-$ radical.

"Effective amount" is means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

"Electron donating group" shall designate a group that will release or donate electrons more than hydrogen would if it occupied the same position in the molecule. See J. March, Advanced Organic Chemistry, 3rd Ed., John Wiley & Sons p. 238 (1985). These types of groups are well known in the art. Examples include alkyl, aralkyl, cycloalkyl, heteroaralkyl, heteroaryl, or heterocyclyl.

"Formulations suitable for nasal or inhalational administration" means formulations which are in a form suitable to be administered nasally or by inhalation to a patient. The formulation may contain a carrier, in a powder form, having a particle size for example in the range 1 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc.) Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents. Inhalational therapy is readily administered by metered dose inhalers.

"Formulations suitable for oral administration" means formulations which are in a form suitable to be administered orally to a patient. The formulations may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-

water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

“Formulations suitable for parenteral administration” means formulations which are in a form suitable to be administered parenterally to a patient. The formulations are sterile and include emulsions, suspensions, aqueous and non-aqueous injection solutions, which may contain suspending agents and thickening agents and anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic, and have a suitably adjusted pH, with the blood of the intended recipient.

“Formulations suitable for rectal administrations” means formulations which are in a form suitable to be administered rectally to a patient. The formulation is preferably in the form of suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

“Formulations suitable for systemic administration” means formulations which are in a form suitable to be administered systemically to a patient. The formulation is preferably administered by injection, including transmuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank’s solution or Ringer’s solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included. Systematic administration also can be by transmucosal or transdermal means, or the compounds can be administered orally. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, bile salts and fusidic acid derivatives for transmucosal administration. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through use of nasal sprays, for example, or suppositories. For oral administration, the compounds are formulated into conventional oral administration forms such as capsules, tablets, and tonics.

“Formulations suitable for topical administration” means formulations which are in a form suitable to be administered topically to a patient. The formulation may be presented as a topical ointment, salves, powders, sprays and inhalants, gels (water or alcohol based), creams, as is generally known in the art, or incorporated into a matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. Formulations suitable for topical administration in the eye include eye drops wherein the active

ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and
5 mouthwashes comprising the active ingredient in a suitable liquid carrier.

"Formulations suitable for vaginal administration" means formulations which are in a form suitable to be administered vaginally to a patient. The formulation may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient
10 such carriers as are known in the art to be appropriate.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

15 "Heteroaralkenyl" means an heteroaryl-alkenyl- group wherein the heteroaryl and alkenyl are as herein described. Preferred heteroaralkenyls contain a lower alkenyl moiety. An exemplary aralkenyl group is 4-pyridylvinyl, thienylethenyl, pyridylethenyl, imidazolylethenyl and pyrazinylethenyl.

20 "Heteroaralkyl" means a heteroaryl-alkyl- group wherein the heteroaryl and alkyl are as herein described. Preferred heteroaralkyls contain a lower alkyl moiety. Exemplary heteroaralkyl groups may contain thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Heteroaralkyloxy" means an heteroaralkyl-O- group wherein the heteroaralkyl group is as herein described. An exemplary heteroaralkyloxy group is 4-pyridylmethyloxy.
25

"Heteroaralkyloxyalkenyl" means an heteroaralkyl-O-alkenyl group wherein the heteroaralkyl and alkenyl groups are as herein described. An exemplary heteroaralkyloxyalkenyl group is 4-pyridylmethyloxyallyl.

30 "Heteroaralkyloxyalkyl" means an heteroaralkyl-O-alkyl group wherein the heteroaralkyl and alkyl groups are as herein described. An exemplary heteroaralkyloxy group is 4-pyridylmethyloxyethyl.

"Heteroaralkynyl" means an heteroaryl-alkynyl- group wherein the heteroaryl and alkynyl are as herein described. Preferred heteroaralkynyls contain a lower alkynyl moiety. Exemplary
35 heteroaralkynyl groups are pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl and 4-pyridylethynyl.

"Heteroaroyl" means an means an heteroaryl-CO- group wherein the heteroaryl group is as herein described. Exemplary groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl and 1- and 2-naphthoyl and pyridinoyl.

5 "Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The "heteroaryl" may also be substituted by one or more "ring system substituents" which may be the same or different,
10 and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. Representative heteroaryl and substituted heteroaryl groups include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, tetrazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl,
15 pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindole, 1,2,4-triazinyl, Preferred heteroaryl groups include pyrazinyl, thienyl, pyridyl, pyrimidinyl, quinolinyl, tetrazolyl, imidazolyl, thiazolyl, benzothienyl, isoxazolyl and
20 isothiazolyl.

"Heteroarylalkenyl" means a heteroaryl-alkenyl-group wherein the heteroaryl and alkenyl moieties are as described herein. Preferred heteroarylalkenyl groups contain a C₂₋₁₂ alkenyl moiety. Exemplary heteroarylalkenyl groups include pyridylpentenyl, pyridylhexenyl and
25 pyridylheptenyl.

"Heteroarylalkynyl" means an aryl-alkynyl- group wherein the heteroaryl and alkynyl moiety are as herein described. Preferred heteroarylalkynyl groups contain a C₂₋₁₂ alkynyl moiety. Exemplary heteroarylalkynyl groups include 3-pyridyl-but-2-ynyl
30 and pyridylpropynyl.

"Heteroaryldiazo" means an heteroaryl -azo- group wherein the heteroaryl and azo groups are as defined herein.

35 "Fused heteroarylcycloalkenyl" means a fused heteroaryl and cycloalkenyl as defined herein. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused heteroarylcycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa

or thia as a prefix before heteroaryl portion of the fused heteroarylcycloalkenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylcycloalkenyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl may also be optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkenyl include 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalyl, 5,6-dihydroquinazolyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like.

"Fused heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl as defined herein. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused heteroarylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcycloalkyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkyl include 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidazole-[4,5]-pyridin-2-onyl, and the like.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heteroaryl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclenyl include 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl,

1,2-dihydro-1,5-naphthyridinyl, 1,2-dihydro-1,6-naphthyridinyl, 1,2-dihydro-1,7-naphthyridinyl, 1,2-dihydro-1,8-naphthyridinyl, 1,2-dihydro-2,6-naphthyridinyl, and the like.

"Fused heteroarylheterocyclyl" means a fused heteroaryl and heterocyclyl as defined herein.

- 5 Preferred fused heteroarylheterocyclyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present
- 10 respectively as a ring atom. The fused heteroarylheterocyclyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heteroaryl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heteroaryl or heterocyclyl portion of the
- 15 fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclyl include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-
- 20 tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5] naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-
- 25 tetrahydro[1,8]naphthyridinyl, 1,2,3,4-tetrahydro[2,6]naphthyridinyl, and the like.

"Heteroarylsulphonylcarbamoyl" means a heteroaryl-SO₂-NH-C(=O)- group wherein the heteroaryl group is as herein described.

- 30 "Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 13 carbon atoms, preferably about 5 to about 13 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The
- 35 designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the

heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, 1,4,4a,5a,6,9,9a,9b-octahydro-dibenzofuran, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2*H*-pyran, dihydrofuranyl, and fluorodihydrofuranyl. Preferred is dihydrofuranyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Preferred monocyclic thiaheterocyclenyl rings include dihydrothiophenyl and dihydrothiopyranyl; more preferred is dihydrothiophenyl. Preferred ring system substituents include amidino, halogen, hydroxy, alkoxycarbonylalkyl, carboxyalkyl or Y¹Y²N- as defined herein.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, 2-thioxo-4-thiazolidinonyl, tetrahydrothiopyranyl, and the like. Preferred heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, piperidyl. Preferred heterocyclyl group substituents include alkyl, aralkyl, amidino, halogen, hydroxy, aralkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl or Y¹Y²N- as defined herein.

"Heterocyclylalkyl" means an heterocyclyl-alkyl- group wherein the heterocyclyl and alkyl are as herein described. Preferred heterocyclylalkyls contain a lower alkyl moiety. An exemplary heteroaralkyl group is tetrahydropyranylmethyl.

"Heterocyclylalkyloxyalkyl" means an heterocyclyl-alkyl-O-alkyl- group wherein the heterocyclyl and alkyls groups independently are as herein described. An exemplary heteroaralkyl group is tetrahydropyranylmethyloxymethyl.

"Heterocyclyloxy" means a heterocyclyl-O- group in which the heterocyclyl group is as previously described. Exemplary heterocyclyloxy groups include quinuclidyloxy, pentamethylenesulfideoxy, tetrahydropyranyloxy, tetrahydrothiophenyloxy, pyrrolidinylloxy,

tetrahydrofuranyloxy or 7-oxabicyclo[2.2.1]heptanyloxy, hydroxytetrahydropyranyloxy and hydroxy-7-oxabicyclo[2.2.1]heptanyloxy.

“Hydrate” means a solvate wherein the solvent molecule(s) is/are H₂O.

5

“Hydroxyalkyl” means a HO-alkyl- group wherein alkyl is as herein defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

10

“Hygroscopicity” means sorption, implying an acquired amount or state of water sufficient to affect the physical or chemical properties of the substance (Eds. J. Swarbrick and J. C. Boylan, Encyclopedia of Pharmaceutical Technology, Vol. 10, p. 33).

15

“Liquid dosage form” means the dose of the active compound to be administered to the patient is in liquid form, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

20

“Modulate” refers to the ability of a compound to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of a ligand from a precursor) induce expression of gene(s) maintained under hormone control, or to repress expression of gene (s) maintained under such control.

25

“Patient” includes both human and other mammals.

30

“Pharmaceutical composition” refers to a composition comprising a compound of formula (I), a compound of formula (II), or a compound of formula (III), and at least one component selected from the group comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured

35

by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin. Examples of suitable carriers, diluents, solvents or vehicles include water, ethanol, polyols, suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, milk sugar, sodium citrate, calcium carbonate, dicalcium phosphate phosphate. Examples of disintegrating agents include starch, alginic acids and certain complex silicates. Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

"Pharmaceutically acceptable" means it is, within the scope of sound medical judgment, suitable for use in contact with the cells of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable dosage forms" refers to dosage forms of the compound of the invention, and includes, for example, tablets, dragees, powders, elixirs, syrups, liquid preparations, including suspensions, sprays, inhalants tablets, lozenges, emulsions, solutions, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, latest edition.

"Pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

"Pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, *in vivo* form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as

acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds of this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion is provided in Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, . K. Widder et al, Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery Reviews, H. Bundgaard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692, 1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, sulphamates, malonates, salicylates, propionates, methylene-bis- β -hydroxynaphthoates, gentisates, isethionates, di-p-toluoyletartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quaternary ammonium salts, and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66: p.1-19 (1977) which is incorporated herein by reference.) Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low

toxicity and acceptability for medical use. ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.


“Solid dosage form” means the dosage form of the compound of the invention is solid form, for example capsules, tablets, pills, powders, dragees or granules. In such solid dosage forms, the compound of the invention is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, (j) opacifying agents, (k) buffering agents, and agents which release the compound(s) of the invention in a certain part of the intestinal tract in a delayed manner.

“Solvate” means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include ethanولات, methanولات, and the like.

“Ring system substituents” mean substituents attached to aromatic or non-aromatic ring systems inclusive of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxy carbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryldiazo, heteroaryldiazo, amidino, Y¹Y²N-, Y¹Y²N-alkyl-, Y¹Y²NCO- or Y¹Y²NSO₂-, wherein Y¹ and Y² are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl or aroyl as

defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is Y^1Y^2NCO- or $Y^1Y^2NSO_2-$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered heterocyclyl or heterocyclenyl. Preferred ring system substituents are alkoxycarbonyl, alkoxy, halo, aryl, aralkoxy, alkyl, hydroxy, aryloxy, nitro, alkylsulfonyl, heteroaryl, Y^1Y^2N- . Most preferred ring system substituents are selected from alkoxycarbonyl, halo, aryl, aralkoxy, aralkyl, alkyl, hydroxy, aryloxy, Y^1Y^2N- , oxo, cyano, nitro, and arylsulfinyl, . When a ring system is saturated or partially saturated, the "ring system substituents" further include , methylene ($H_2C=$), oxo ($O=$), thioxo ($S=$).

"Solid support" means a substrate which is inert to the reagents and reaction conditions described herein, as well as being substantially insoluble in the media used. Representative solid supports include inorganic substrates such as kieselguhr, silica gel, and controlled pore glass; organic polymers including polystyrene, polypropylene, polyethylene glycol, polyacrylamide, cellulose, and the like; and composite inorganic/polymeric compositions such as polyacrylamide supported within a matrix of kieselguhr particles. See J.M. Stewart and J.D. Young, *Solid Phase Peptide Synthesis*, 2nd. Ed., Pierce Chemical Co. (Chicago, IL, 1984). In addition, "solid support" includes a solid support as described above which is affixed to a second inert support such as the pins described herein which comprise a detachable polyethylene- or polypropylene-base head grafted with an amino functionalized methacrylate copolymer and an inert stem. In addition, "solid support" includes polymeric supports such as the polyethylene glycol supports described by Janda et al., *Proc. Natl. Acad. Sci. USA*, 92, 6419-6423 (1995) and S. Brenner, WO 95/16918, which are soluble in many solvents but can be precipitated by the addition of a precipitating solvent.

"Resin" means a solid support as defined above which is chemically modified as is known in the art to incorporate a plurality of reactive groups, such as hydroxyl, amino or isocyanate moieties. groups are covalently bound directly to the solid support or attached to the solid support by covalent bonds through a linking group. The resins used in this invention are designated as , which designates a solid support optionally bearing a linking group which can be directly bound or through the linking group thereof to a reaction component in the method according to the invention.

" Y^1Y^2N- " means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as herein described. Exemplary groups include amino (H_2N-), methylamino, dimethylamino, diethylamino, pyrrolidine, piperidine, benzylamino, or phenethylamino.

" Y^1Y^2NCO- " means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as herein described. Exemplary groups are carbamoyl (H_2NCO-) and dimethylaminocarbamoyl (Me_2NCO-).

"Y¹Y²NSO₂-" means a substituted or unsubstituted sulfamoyl group, wherein Y¹ and Y² are as herein described. Exemplary groups are aminosulfamoyl (H₂NSO₂-) and dimethylaminosulfamoyl (Me₂NSO₂-).

5 "Primary or secondary protected amine" means a group of the following formula Y^aY^bN- wherein one of Y^a and Y^b is P^a a nitrogen protecting group and the other of Y^a and Y^b is hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroarylcyloalkenyl, fused heteroarylcyloalkyl, fused heteroarylheterocyclenyl, fused heteroarylheterocyclyl, heterocyclenyl or
10 heterocyclyl.

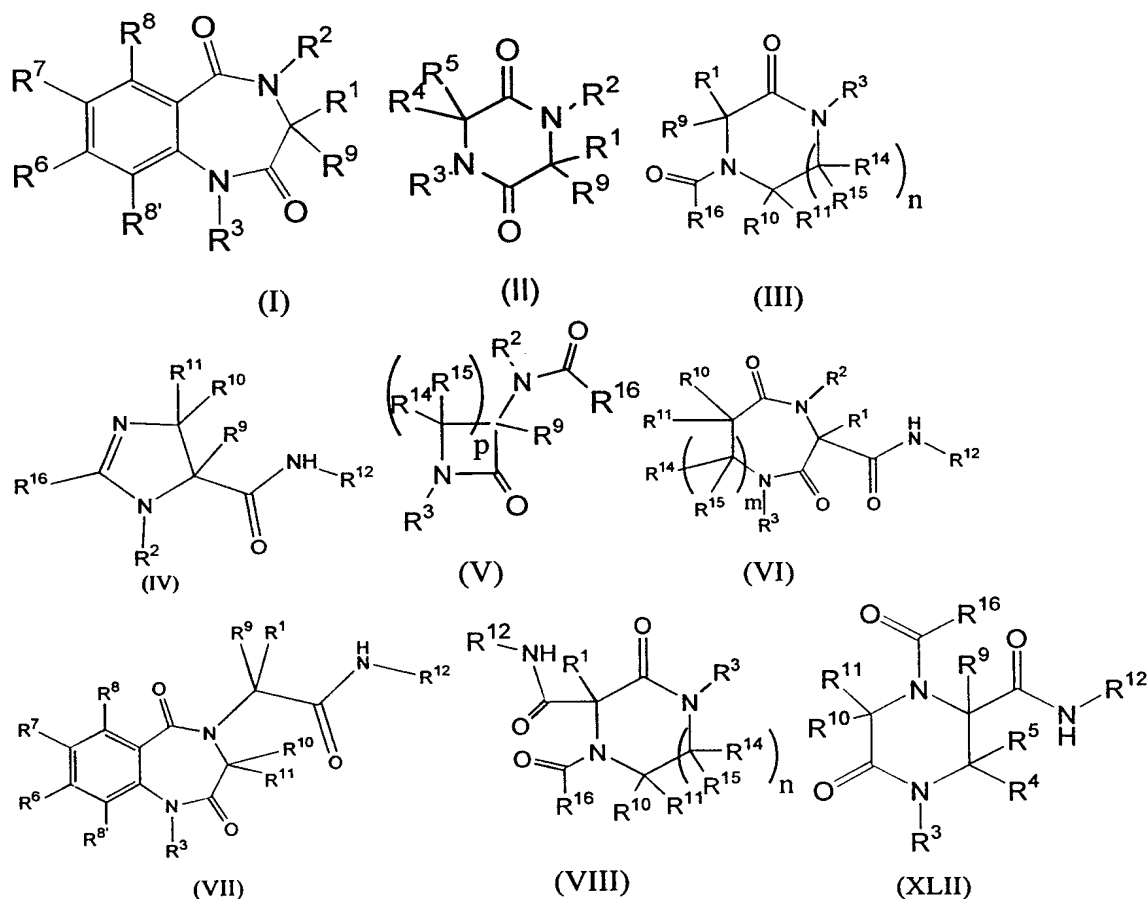
"Activated carboxylic acid" means a group of the following formula LO-CO- wherein L is aliphatic, aromatic or a resin moiety.

15 In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

Preferred Embodiments

20 One particular aspect of the present invention is directed to a method for preparing a cyclized compound selected from group of formulae consisting of 1,4-benzodiazepine-2,5-dione derivatives of general formulae (I), and (VII), diketopiperazine derivatives of general formula (II), ketopiperazine derivatives and dihydroquinoxalinone derivatives of general formula (III) and (VIII), dihydroimidazole derivatives of general formula (IV), lactam derivatives of general formula (V), 1,4-benzodiazepine-2,5-
25 dione diketopiperazine derivatives of formula (VI), and ketopiperazine derivatives of formula (XLII):-.

29



5

wherein:

 $n = 1$ or 2 ; $m = 0$ or 1 ; $p = 2$;

10 R^1 and R^9 independently represent hydrogen, alkenyl, alkyl, aralkenyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl, or heterocyclyl;

15

R^2 represents hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl;

20

R³ represents hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl.

5

R⁴ or R⁵ independently represent hydrogen, alkenyl, alkyl, aryl, alkynyl, aralkenyl, aralkynyl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaralkenyl, heteroaralkynyl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or

10 cycloalkenyl, heterocyclyl, heterocyclenyl, or

R⁴ and R⁵ taken together with the carbon atom through which R⁴ and R⁵ are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl;

R⁶, R⁷, R⁸ and R^{8'} independently represent hydrogen, alkenyl, alkenyloxy, alkoxy, alkyl, aryl,

15 alkylsulfinylcarbamoyl, alkynyl, alkynyloxy, aralkenyl, aralkylsulfonyl, aralkynyl, fused
arylcyaloalkenyl, fused arylcyaloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl,
aryloxycarbonyl, cycloalkyloxy, heteroaralkenyl, heteroaralkyloxy, heteroaralkynyl, heteroaroyl, fused
heteroarylcyaloalkenyl, fused heteroarylcyaloalkyl, fused heteroarylheterocyclenyl, fused
heteroarylheterocyclyl, heteroarylsulphonylcarbamoyl, heterocyclyloxy, heteroaryl, aralkyl,

20 heteroaralkyl, hydroxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryldiazo, heteroaryldiazo, amidino, Y¹Y²N-, Y¹Y²NCO- or Y¹Y²NSO₂-, wherein Y¹ and Y² are independently hydrogen, alkyl, aryl, aralkyl or

25 heteroaralkyl, or where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl or aroyl and the other of Y¹ and Y² is as defined previously, or where the substituent is Y¹Y²NCO- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked form a 4 to 7 membered heterocyclyl or heterocyclenyl, or

R³ and R⁸ taken together with the nitrogen atom and carbon atoms through which R³ and R⁸ are linked form a 5 to 7 membered heterocyclyl or heterocyclenyl, or two adjacent substituents selected from the substituents R⁶, R⁷, R⁸ and R⁸ taken together with the aryl carbon atoms through which the two adjacent substituents are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl, or 6 membered aryl or 5 to 6 membered heteroaryl;

35 R¹⁴, R¹⁵, R¹⁰ and R¹¹ independently represent hydrogen, alkenyl, alkyl, aryl, alkynyl, aralkenyl, aralkynyl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaralkenyl, heteroaralkynyl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused

heteroarylheterocyclenyl, fused heteroarylheterocyclyl, heteroarylsulphonylcarbamoyl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or

when n=1, R¹¹ and R¹⁴ are absent and R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl;

or when n=1, R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl;

or when n=2, adjacent R¹¹ and R¹⁴ are absent and R¹⁰ and adjacent R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl;

or when n=2, R¹⁰ and adjacent R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclyenyl;

or when n or p =2, adjacent R¹⁴ and R¹⁴ are absent and adjacent R¹⁵ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl;

or when n or p =2, adjacent R¹⁵ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl;

or when m=1, R¹¹ and R¹⁴ are absent and R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl;

or when m=1, R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl;

R¹² represents alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl;

R¹⁶ represents hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, heteroaralkenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl.

In one aspect, this invention is directed to a solution phase synthesis of a compound of formula (I) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., *Angew. Chem. Int. Ed. Engl.*, 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula (XIV), with an aldehyde or ketone of formula (XV), an amine of formula (XVI), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XVII) and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (I). Hulme, C.; Tang, S-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, 63, 8021.

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (I) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula (XIV), with an aldehyde or ketone of formula (XV), an amine of formula (XVI), and a resin bound
5 isonitrile selected from (IXa) or (XVIII) to form the respective intermediate resin bound compound and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (I).

In another aspect, this invention is directed to a solution phase synthesis of a compound of
10 formula (II) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula (XXII) with an aldehyde or ketone of formula (XV), an amine of formula (XVI), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XXIII) and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (II).

15 Hulme, C.; Morrisette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, 39, 113.

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (II) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula
20 (XXII) with an aldehyde or ketone of formula (XV), an amine of formula (XVI), and a resin bound isonitrile selected from (IXa) or (XVIII) to form the respective intermediate resin bound compound and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (II).

25 In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (III) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with an aldehyde or ketone of formula (XV), an diamine of formula (XXVII), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XXVIII) and nitrogen-deprotection of the
30 intermediate compound and cyclization to form a compound of formula (III). Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolkowski, P.; Kumar, N. V. *Tetrahedron Lett.* **39**, 7227.

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (III) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I.,
35 Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with an aldehyde or ketone of formula (XV), a diamine of formula (XXVII), and a resin bound isonitrile selected from (IXa) or (XVIII) to form the respective intermediate resin bound compound and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (III).

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (IV) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an nitrogen-protected amino aldehyde of formula (XXXIII) with acid of formula (XXVI), an amine of formula (XVI), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XXXIV) and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (IV). The non-cyclized amines were removed via a solution phase scavenging step with the simultaneous addition of PS-DIEA or PS-tris(2-aminoethyl)amine (6 equiv.) and PS-NCO (3 equiv.) in dichloroethane. (Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. Flynn, D.L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodward, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. Purchased from Argonaut[®] technologies (PS-DIEA - polystyrene bound diisopropylethylamine)).

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (VI) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting compound of formula (XXXVII), with an acid of formula (XIV), an amine of formula (XVI), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XXXVIII) and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VI).

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (V) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino aldehyde or ketone of formula (XXXV), an amine of formula (XVI), an acid of formula (XXVI) and a resin bound isonitrile selected from (IXa) or (XVIII) to form the respective intermediate resin bound compound and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (V).

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (VI) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an nitrogen-protected amino acid of formula (XIV) with an aldehyde or ketone of formula (XXXVII), an amine of formula (XVI), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XXXVIII) and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VI).

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (VI) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an nitrogen-protected amino acid of formula (XIV) with an aldehyde or ketone of formula (XXXVII), an amine of formula (XVI), and a resin bound isonitrile of formula (XVIII) to form an intermediate compound and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VI).

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (VII) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting nitrogen-protected amino acid of formula (XIV), a suitable non-resin bound α -amino ester, a non-resin bound isonitrile (IX), and an aldehyde or ketone of formula (XV), to form an intermediate compound and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VIII).

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (VII) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula (XIV), a resin bound α -amino ester of formula (XXXIX), and a non-resin bound isonitrile (IX) and an aldehyde or ketone of formula (XV), to form the intermediate resin bound compound (XL) and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (VII).

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (VIII) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with (XXXVII), a diamine of formula (XXVII), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XLI) and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VIII).

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (VIII) via a '2-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with (XXXVII), a diamine of formula (XXVIIa), and a resin bound isonitrile of formula (IXa) or (XVIII) to form an intermediate and cyclization to form a compound of formula (VIII), wherein R¹² represents the resin bound isonitrile derivative.

In another aspect, this invention is directed to a solution phase synthesis of a compound of formula (VIII) via a '2-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with

35

(XXXVII), a diamine of formula (XXVIIa), and a non resin bound isonitrile of formula (IX) to form an intermediate compound of formula (XLI) and cyclization to form a compound of formula (VIII).

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (VIII) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting an acid of formula (XXVI) with (XXXVII), a diamine of formula (XXVII), and a resin bound isonitrile of formula (IXa) or (XVIII) to form an intermediate and nitrogen-deprotection of the intermediate compound and cyclization to form a compound of formula (VIII), wherein R¹² represents the resin bound isonitrile derivative.

In another aspect, this invention is directed to a solid phase synthesis of a compound of formula (XLII) via a '3-step, one pot' procedure, employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) combining reacting a nitrogen-protected amino acid of formula (XLIII), a resin bound α -amino ester of formula (XXXIX), and a non-resin bound isonitrile (IX) and an acid of formula (XXVI), to form the intermediate resin bound compound (XLIX) and nitrogen-deprotection of the intermediate compound and cyclization to form the compound of formula (XLII).

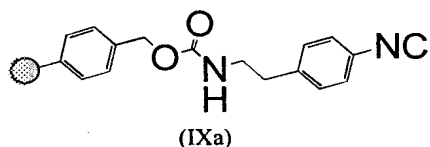
In another aspect, this invention is directed to the preparation of 1,4-benzodiazepine-2,5-dione derivatives of general formulae (I) and (VI), diketopiperazine derivatives of general formula (II), ketopiperazine derivatives and dihydroquinoxalinone derivatives of general formula (III) and (VIII), dihydroimidazole derivatives of general formula (IV), lactam derivatives of general formula (V), by solid phase synthesis employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) using an isonitrile functionalized polymer resin linker (IXa) as described herein, followed by amine deprotection, cleavage from the resin and cyclization. The alkoxide and hydroxide safety-catch clipping strategy and subsequent solution phase cyclization offers similar advantages to a traceless linker (Plunkett, M.J.; Ellman, J.A. *J. Org. Chem.* 1995, 60, 6006; Hulme, C.; Peng, J.; Morton, G.; Salvino, J.M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* 1998, 39,) in that no constant functionality derived from clipping remains at the end of the synthetic protocol.

In another aspect, this invention is directed to the preparation of ketopiperazine derivatives of general formula (XLII) and 1,4-benzodiazepine-2,5-dione derivatives of general formula (VII), by solid phase synthesis employing the Ugi multi-component reaction (MCR) (Ugi, I., Angew. Chem. Int. Ed. Engl., 1962, 1, 8) using an amino ester bound polymer resin linker (XXXIX) as described herein, followed by amine deprotection, cleavage from the resin and cyclization.

In another aspect, this invention is directed to the preparation and use of a novel resin bound isonitrile (IXa), deployed as a novel safety catch linker (Backes, B. J., Virgilio, A. A., Ellman, J. A. *J. Am. Chem. Soc.* 1996, 118, 3055; Kenner, G. W., McDermott, J. R., Sheppard, R. C. *J. Chem. Soc.*,

Chem. Commun. 1971, 636.) in the preparation of 1,4-benzodiazepine-2,5-dione derivatives of general formulae (I), (VI) and (VII), diketopiperazine derivatives of general formula (II), ketopiperazine derivatives and dihydroquinoxalinone derivatives of general formula (III) and (VIII), dihydroimidazole or imidazoline derivatives of general formula (IV), and lactam derivatives of general formula (V).

5



A preferred aspect of the compound of the invention are those wherein:

 $n = 1$ or 2 .

10

A preferred aspect of the compound of the invention are those wherein:

$$m = 0 \text{ or } 1.$$

A preferred aspect of the compound of the invention are those wherein:

15 R' is aralkyl, alkyl, aryl, heteroaryl, cycloalkyl, aralkenyl, heterocyclenyl or heterocyclyl.

A preferred aspect of the compound of the invention are those wherein:

R¹ is hydrogen or alkyl.

20 A preferred aspect of the compound of the invention are those wherein:

R² represents heteroaralkyl, aralkyl, alkyl, fused arylcycloalkyl, cycloalkyl, heterocyclyl, aryl, fused arylheterocyclenyl, or fused arylheterocyclyl.

A preferred aspect of the compound of the invention are those wherein:

25 R³ represents hydrogen, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl, or heterocyclyl

30 A preferred aspect of the compound of the invention are those wherein:

R⁴ and R⁵ independently represents hydrogen, alkyl, aralkyl, aryl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, heterocyclenyl or heterocyclyl.

A preferred aspect of the compound of the invention are those wherein:

R⁶, R⁷, R⁸ and R^{8'} independently represents hydrogen, alkenyl, alkyl, aryl, aralkyl, heteroaralkyl, hydroxy, aryloxy, alkoxy, aralkoxy, halo, nitro, cyano, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, fused heteroaryl-cycloalkenyl, fused heteroaryl-cycloalkyl, fused heteroarylheterocyclenyl, fused heteroarylheterocyclyl, fused heteroaryl-cycloalkenyl, fused heteroaryl-cycloalkyl, fused heteroarylheterocyclenyl, fused heteroarylheterocyclyl, heteroarylsulphonylcarbamoyl, heteroaryl, Y¹Y²N-, or Y¹Y²NSO₂-.

A preferred aspect of the compound of the invention are those wherein:

R¹⁵ is absent and R³ and R¹⁴ taken together with the nitrogen atom and carbon atom through which R³ and R¹⁴ are linked to form a 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein:

R⁴ and R⁵ taken together with the carbon atom through which R⁴ and R⁵ are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl.

A preferred aspect of the compound of the invention are those wherein:

two adjacent substituents selected from the substituents R⁶, R⁷, R^{8'} and R⁸ taken together with the aryl carbon atoms through which the two adjacent substituents are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl, or 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein:

R¹⁰, R¹¹, R¹⁴ and R¹⁵ independently represent hydrogen, alkyl, heteroaralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or aralkyl.

A preferred aspect of the compound of the invention are those wherein:

n=1, R¹¹ and R¹⁴ are absent and R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein:

n=1, R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl.

A preferred aspect of the compound of the invention are those wherein

n=2, adjacent R¹¹ and R¹⁴ are absent and R¹⁰ and adjacent R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein

n=2, R¹⁰ and adjacent R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl.

A preferred aspect of the compound of the invention are those wherein

- 5 n or p =2, adjacent R¹⁴ and R¹⁴ are absent and adjacent R¹⁵ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein

- 10 n or p =2, adjacent R¹⁵ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl.

A preferred aspect of the compound of the invention are those wherein

- 15 m=1, R¹¹ and R¹⁴ are absent and R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 6 membered aryl or 5 to 6 membered heteroaryl.

A preferred aspect of the compound of the invention are those wherein

- m=1, R¹⁰ and R¹⁵ taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered cycloalkyl or a cycloalkenyl, heterocyclyl or heterocyclenyl.

A preferred aspect of the compound of the invention are those wherein:

- 20 R¹⁶ represents hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, heteroaralkenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused arylcycloalkyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl.

A preferred aspect of the compound of the invention are those wherein:

- 25 R¹⁶ represents alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, heteroaralkenyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl.

A more preferred aspect of the compound of the invention are those wherein:

n = 1.

A more preferred aspect of the compound of the invention are those wherein:

n = 2.

A more preferred aspect of the compound of the invention are those wherein:

m = 0.

A more preferred aspect of the compound of the invention are those wherein:

m = 1.

5

A more preferred aspect of the compound of the invention are those wherein:

R⁹ is hydrogen.

A more preferred aspect of the compound of the invention are those wherein:

10 R⁹ is alkyl.

A more preferred aspect of the compound of the invention are those wherein:

R¹ is aralkyl, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

15

A more preferred aspect of the compound of the invention are those wherein:

R² represents aralkyl, alkyl, fused arylheterocyclenyl, or fused arylheterocyclyl.

A more preferred aspect of the compound of the invention are those wherein:

R³ represents hydrogen, alkyl, aralkyl, cycloalkyl, cycloalkenyl, heteroaralkyl or heterocyclenyl,
20 heterocyclyl.

A more preferred aspect of the compound of the invention are those wherein:

R³ represents hydrogen.

25

A most preferred aspect of the compound of the invention are those wherein:

R⁴ and R⁵ independently represents alkyl, aralkyl, heteroaralkyl, heterocyclyl, or cycloalkyl.

A more preferred aspect of the compound of the invention are those wherein:

30 R⁶, R⁷ R⁸ and R⁸, independently represents hydrogen, halo, alkoxy, alkyl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, or heteroaryl.

A more preferred aspect of the compound of the invention are those wherein:

R¹⁰, R¹¹, R¹⁴ and R¹⁵ independently represent hydrogen, alkyl, or aralkyl.

35

A more preferred aspect of the compound of the invention are those wherein:

R¹² represents alkyl, aralkyl, aryl, cycloalkyl, or heterocyclyl.

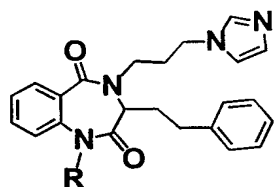
A more preferred aspect of the compound of the invention are those wherein:

R¹⁶ represents alkyl, fused arylheterocyclyl, aralkyl, cycloalkyl, heteroaryl, aryl, heteroaralkyl, alkenyl, heteroaralkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused heteroarylcyloalkenyl, fused heteroarylheterocyclyl, heterocyclenyl or heterocyclyl.

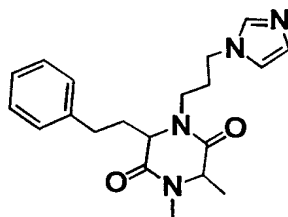
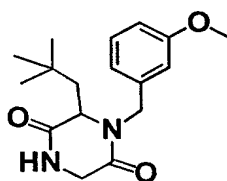
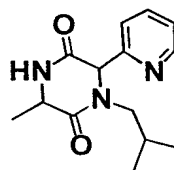
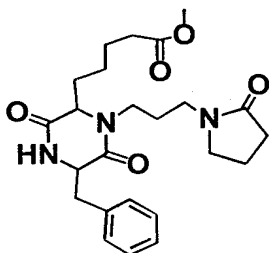
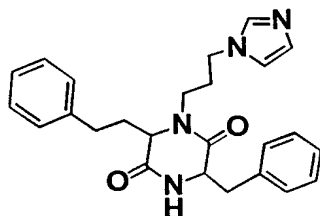
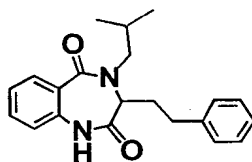
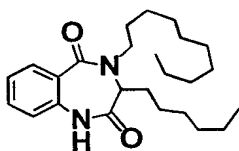
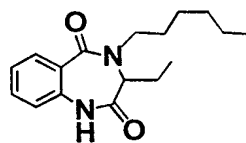
41

A preferred compound according to the invention is selected from the group of formulae consisting of:

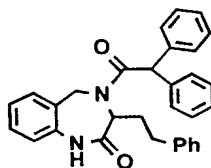
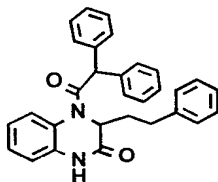
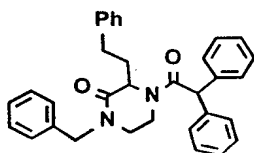
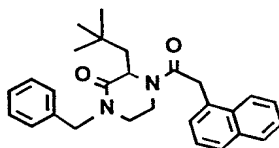
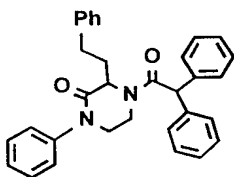
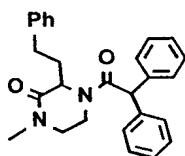
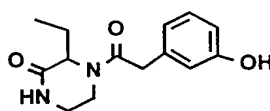
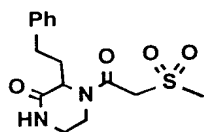
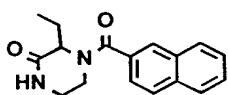
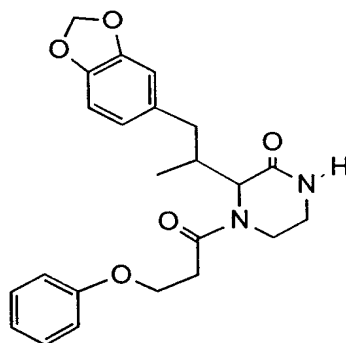
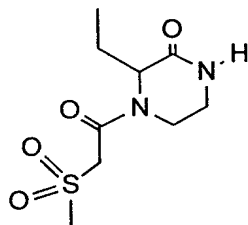
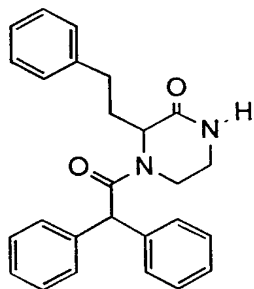
5



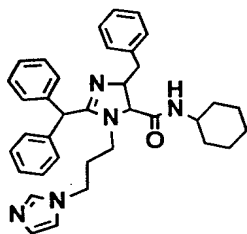
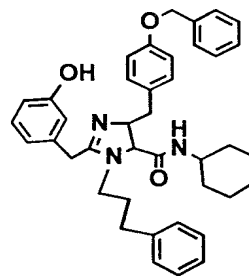
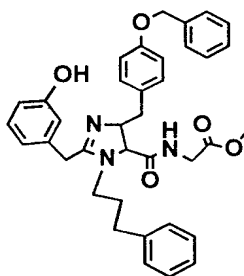
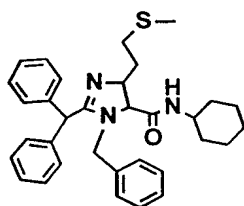
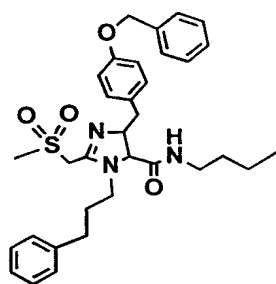
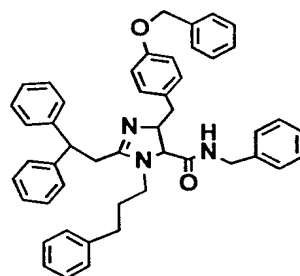
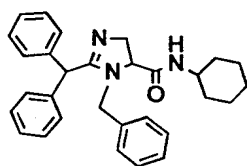
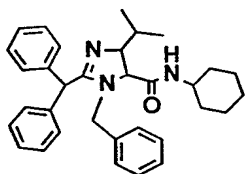
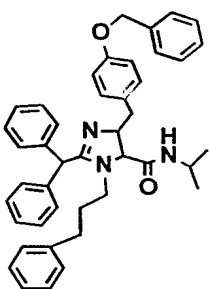
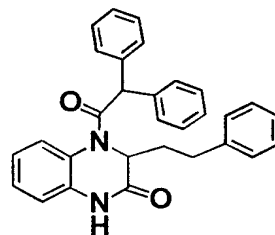
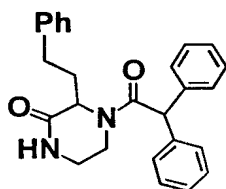
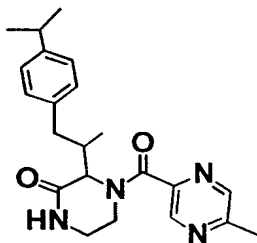
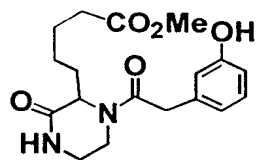
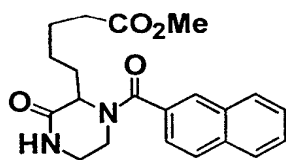
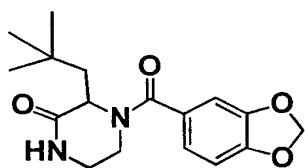
for R=H, or CH₃



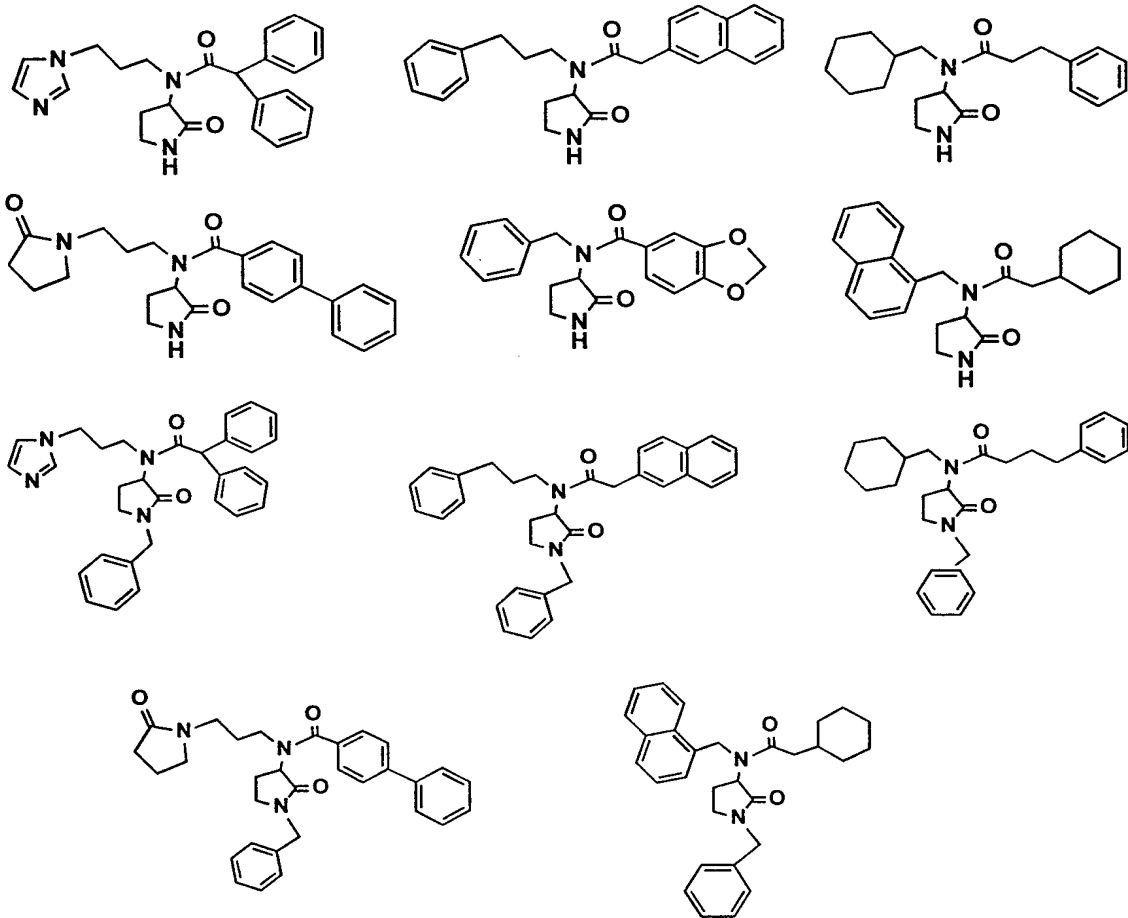
42



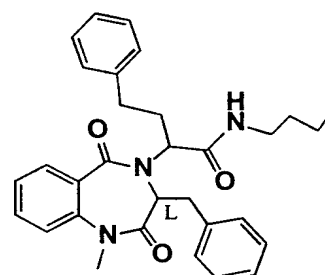
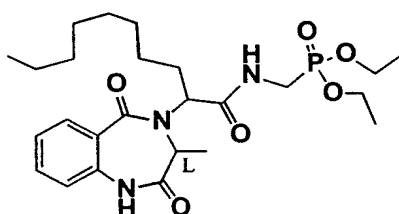
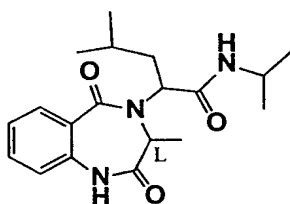
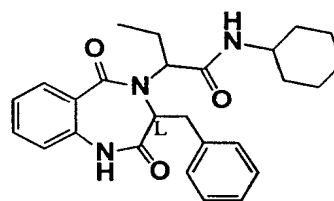
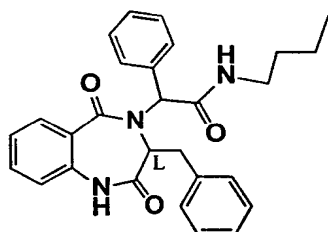
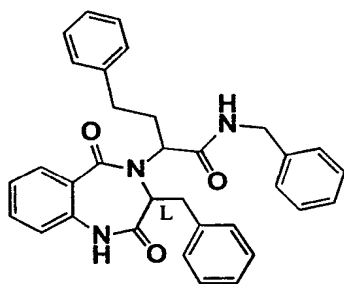
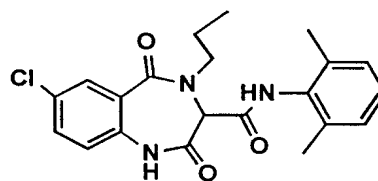
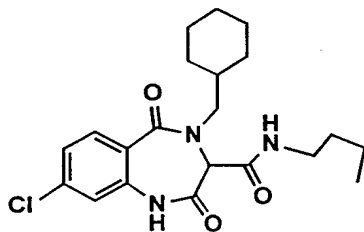
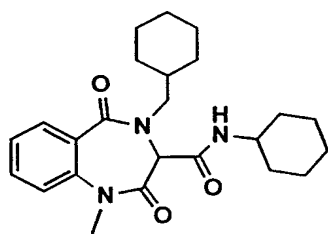
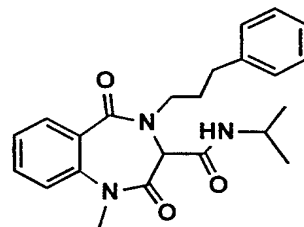
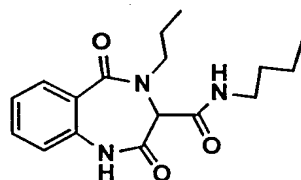
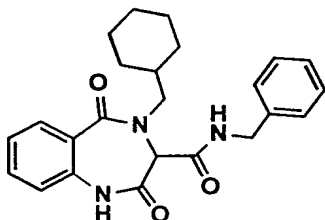
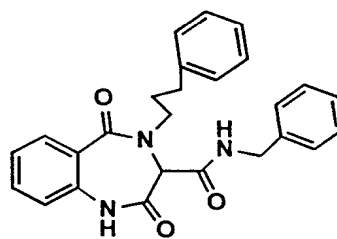
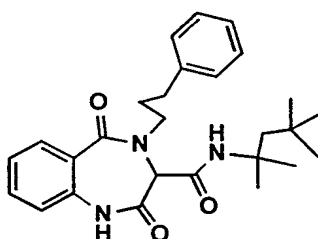
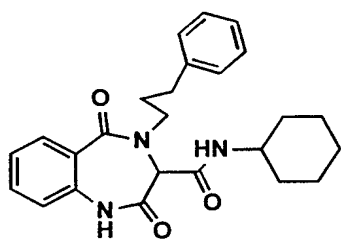
43



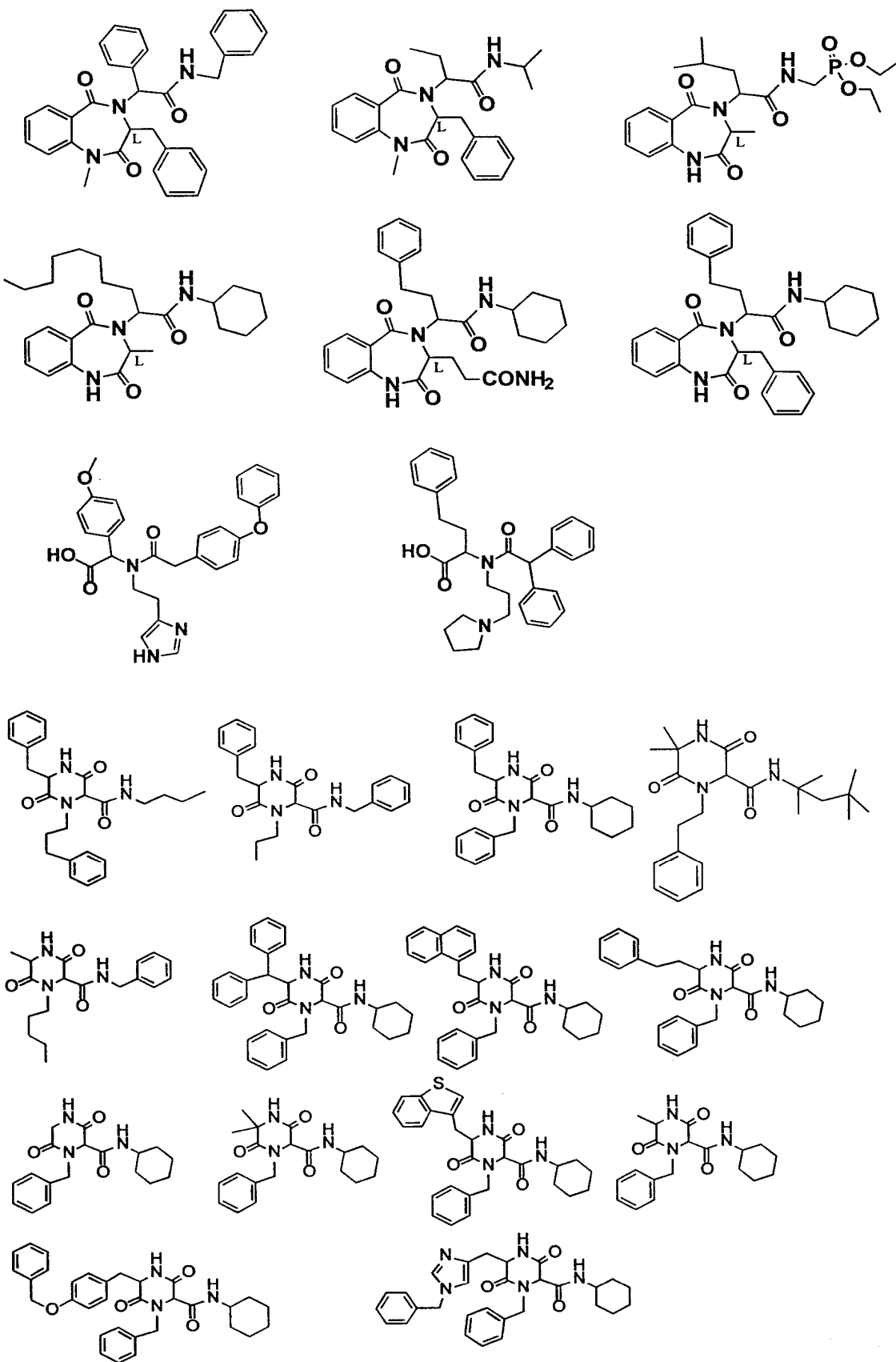
44



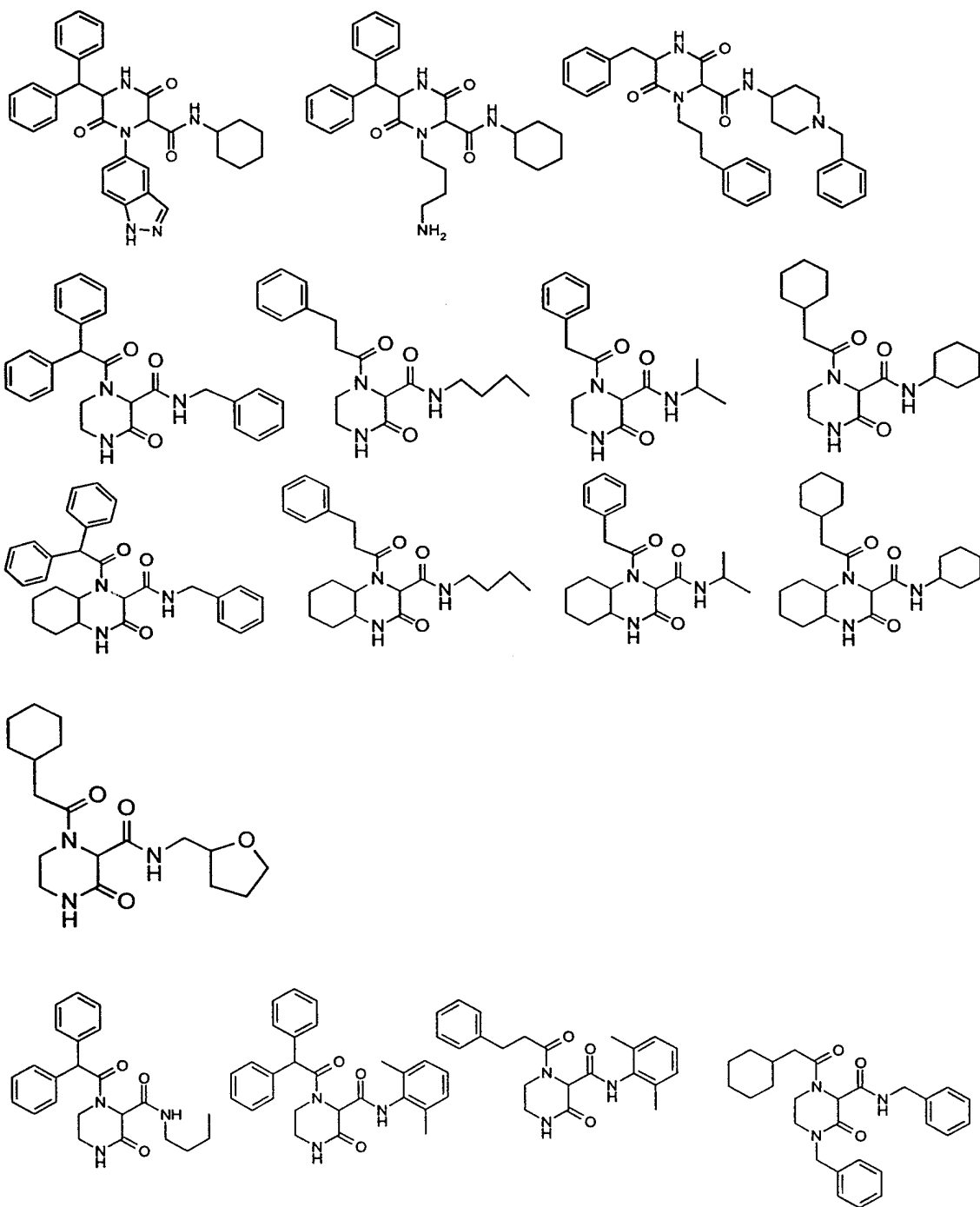
45



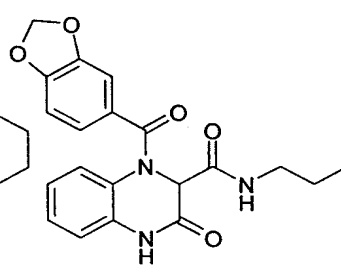
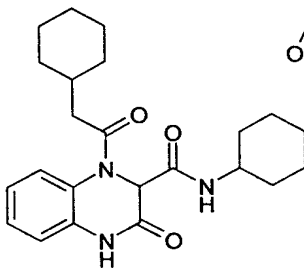
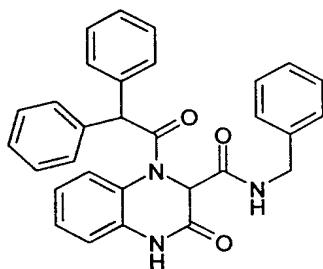
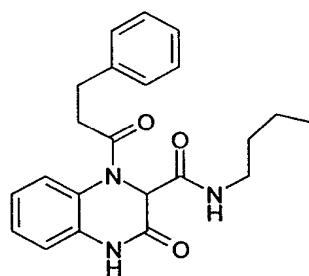
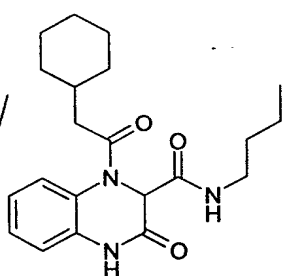
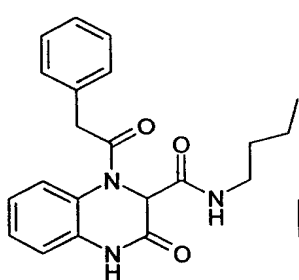
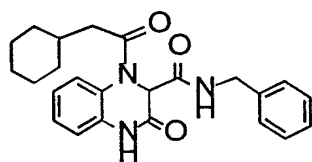
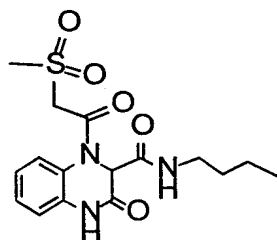
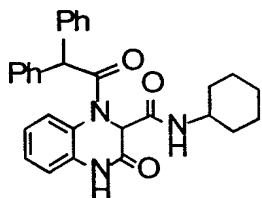
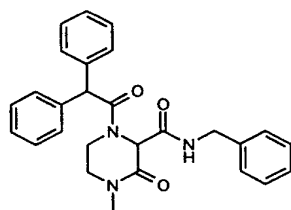
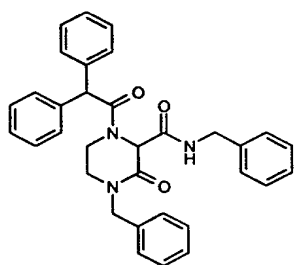
46



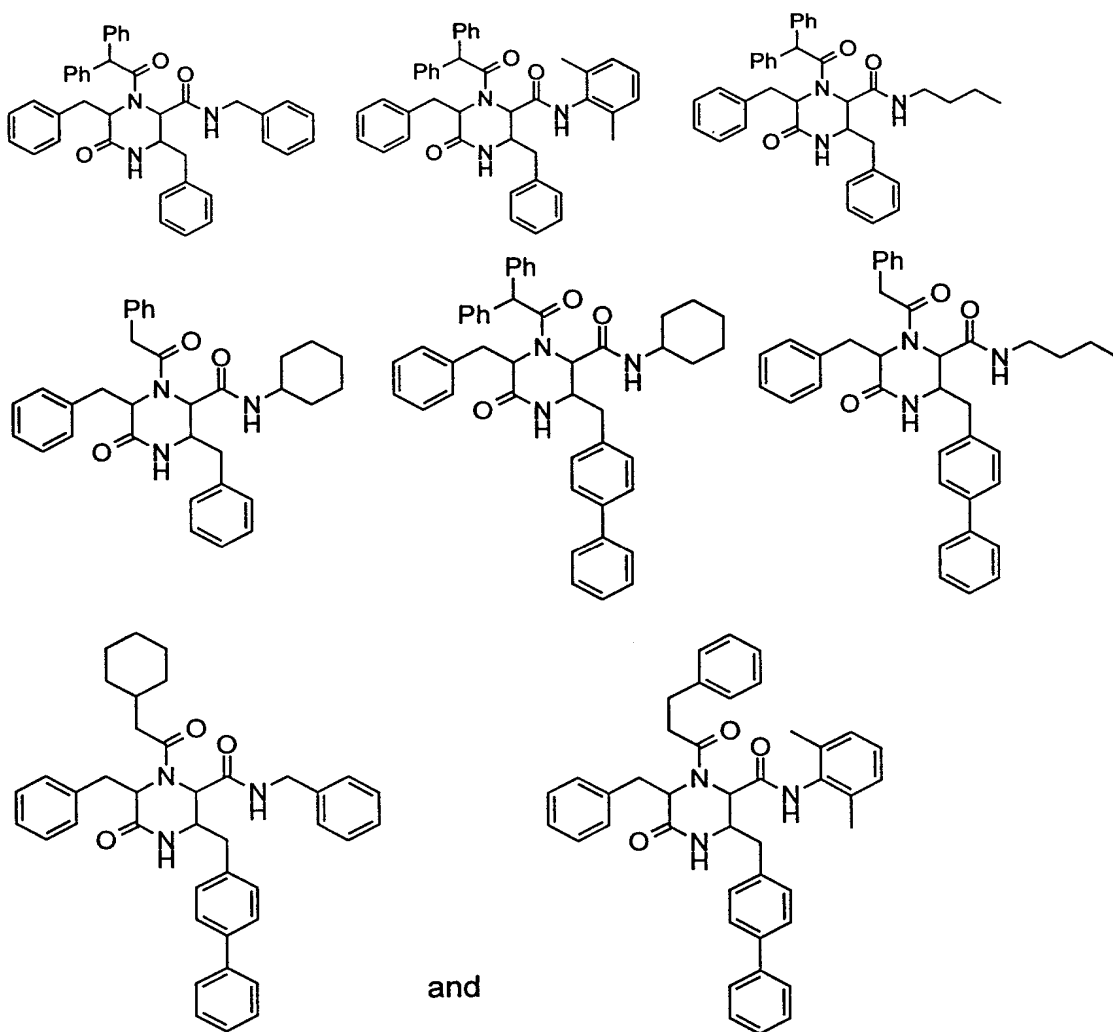
47



48



49



5 It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

10 It is a further object of the invention to provide kits having a plurality of active ingredients (with or without carrier) which, together, may be effectively utilized for carrying out the novel combination therapies of the invention.

15 It is another object of the invention to provide novel pharmaceutical compositions which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

The compounds of the invention optionally are supplied as salts. Those salts which are pharmaceutically acceptable are of particular interest since they are useful in administering the foregoing

compounds for medical purposes. Salts which are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of this invention. The latter is particularly true of amine salts prepared from optically active amines.

5

Where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form.

10

Also, where the compound of the invention contains a basic group, or a sufficiently basic bioisostere, acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form.

15

The foregoing compounds of the invention may also be mixed another therapeutic compound to form pharmaceutical compositions (with or without diluent or carrier) which, when administered, provide simultaneous administration of a combination of active ingredients resulting in the combination therapy of the invention.

20

While it is possible for the compounds of the invention to be administered alone it is preferably to present them as pharmaceutical compositions. The pharmaceutical compositions, both for veterinary and for human use, of the present invention comprise at least one compound of the invention, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients.

25

In certain preferred embodiments, active ingredients necessary in combination therapy may be combined in a single pharmaceutical composition for simultaneous administration.

30

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

35

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the emulsifying wax, and the way together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulgents and emulsion stabilizers suitable for use in the formulation of the present invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof.

The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Solid compositions may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.

The pharmaceutical compositions can be administered in a suitable formulation to humans and animals by topical or systemic administration, including oral, inhalational, rectal, nasal, buccal, sublingual, vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

The formulations can be prepared in unit dosage form by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compounds moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

If desired, and for more effective distribution, the compounds can be microencapsulated in, or attached to, a slow release or targeted delivery systems such as a biocompatible, biodegradable polymer matrices (e.g. poly(d,l-lactide co-glycolide)), liposomes, and microspheres and subcutaneously or intramuscularly injected by a technique called subcutaneous or intramuscular depot to provide continuous slow release of the compound(s) for a period of 2 weeks or longer. The compounds may be sterilized, for example, by filtration through a bacteria retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Actual dosage levels of active ingredient in the compositions of the invention may be varied so as to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

Total daily dose of the compounds of this invention administered to a host in single or divided doses may be in amounts, for example, of from about 0.001 to about 100 mg/kg body weight daily and preferably 0.01 to 10 mg/kg/day. Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body

53

weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular disease being treated.

The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

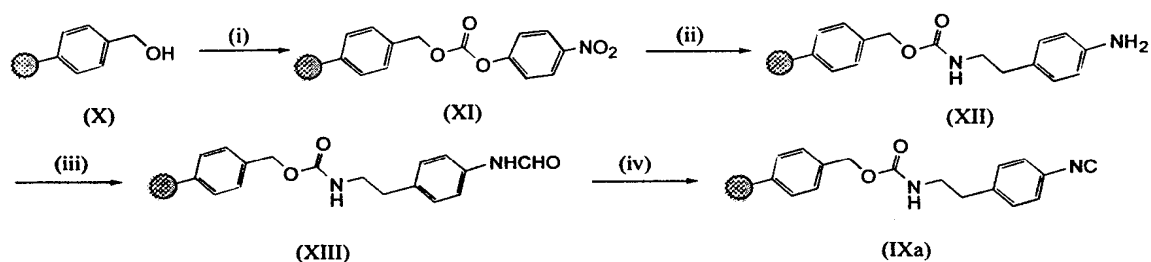
Preparation of Compounds of the Invention

The starting materials and intermediates of compounds of the invention may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991; J. F. W. McOmie in "Protective Groups in Organic Chemistry" Plenum Press, 1973.

General methodology for the preparation the isonitrile resin linker (IXa)



Reagents and Conditions:- (i) Wang resin, 4-nitrophenylchloroformate (5 equiv.), *n*-methyl morpholine (10 equiv.), THF. (ii) 2-(4 amino phenyl)ethylamine (5 equiv.), DMF. (iii) Formic acid (excess), acetic anhydride (excess), CH₂Cl₂ (iv) Ph₃P (5 equiv.), CCl₄ (5 equiv.), Et₃N (5 equiv.), CH₂Cl₂.

5 Experimental Procedures

Nitrocarbonate Resin (XI) :

Wang resin (X) (100.0 g, 109.0 mmol) was swelled in anhydrous THF (1500 ml). N-methyl morpholine (119.8 ml, 1090.0 mmol) and 4-nitrophenyl chloroformate (109.86 g, 545 mmol) were added sequentially. The reaction was cooled in an ice bath for several minutes to quench the slightly exothermic reaction. The ice bath was then removed and the reaction was allowed to warm to RT. It was mixed on an orbital shaker at RT overnight. The reaction solution was drained off and the resin was washed with THF (5X), 20% H₂O in DMF (5X), DMF (5X), THF (5X), and Et₂O (5x). The resin product (XI) was then placed in a vacuum oven at RT overnight to dry. IR analysis showed two sharp peaks at 1520 cm⁻¹ and 1350 cm⁻¹ for the NO₂ group.

Aniline Resin (XII)

The nitrocarbonate resin (XI) (115.0 g, 125.35 mmol) was swelled in anhydrous DMF (1250 ml). 2-(4-Aminophenyl)ethylamine (82.6 ml, 626.75 mmol) was added to the resin slurry. The reaction was mixed on an orbital shaker at RT overnight. The reaction solution was drained off and the resin was washed with DMF (8X). The still swollen resin was suspended in anhydrous DMF (1000 ml) and a second coupling of the amine (82.6 ml) was run overnight. After draining and washing with DMF (8X) a third coupling was run overnight. The final reaction solution was drained off and the resin product (XII) was washed with DMF (10X), THF (10X), and Et₂O (10X). The resin was then dried in a vacuum oven at RT overnight. IR analysis showed loss of the NO₂ peaks.

Formamide Resin (XIII):

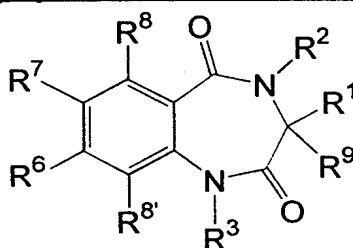
The aniline resin (XII) (109.0 g, 86.1 mmol) was swelled in anhydrous CH₂Cl₂ (1000 ml). Formic acid (500 ml) and acetic anhydride (500 ml) were combined and the resulting exothermic reaction was cooled in an ice bath. Once at RT, the resulting solution was allowed to sit at RT for 40 minutes. This mixed anhydride solution was then added to the resin slurry. The reaction was mixed on an orbital shaker at RT overnight. The reaction solution was drained off and the resin was washed with CH₂Cl₂ (10X). To remove any remaining acetic acid, the resin was washed with 20% H₂O in THF (6X) until the washings were neutral to litmus paper. The resin product (XIII) was finally washed with THF (10X) and Et₂O (8X) and then dried in a vacuum oven at RT overnight. IR analysis showed a strong carbonyl stretch for the formamide at 1698 cm⁻¹.

Isonitrile Resin (IXa) :

55

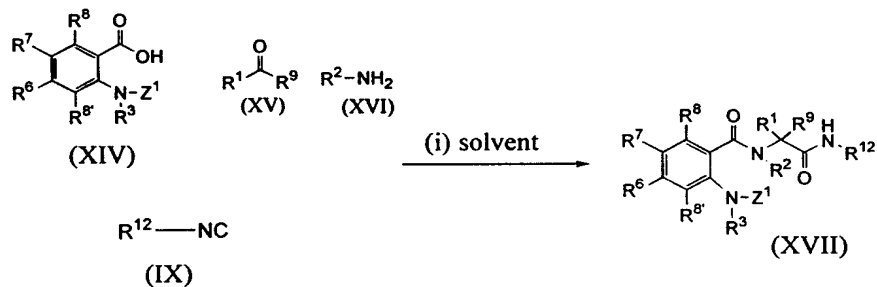
The formamide resin (XIII) (50.0 g, 44.5 mmol) was swelled in anhydrous CH_2Cl_2 (500 ml). Triphenylphosphine (58.4 g, 222.5 mmol), carbon tetrachloride (21.5 ml, 222.5 mmol), and triethylamine (31.0 ml, 222.5 mmol) were added sequentially at RT. The reaction was mixed on an orbital shaker for 4.5 hours at RT. The reaction solution was drained off and the resin product (IXa) was washed with CH_2Cl_2 (20X), THF (10X), and Et_2O (10X). The resin was then placed in a vacuum oven at RT overnight to dry. IR analysis showed a sharp peak for the isonitrile at 2121 cm^{-1} .

General methodology for the preparation of 1,4-Benzodiazepine-2,5-diones (I)



(I)

In general terms, compounds of formula (I) wherein R¹, R², R³, R⁸, R⁶, R⁷, R⁸ and R⁹ are hereinbefore defined, may be synthesized by reacting a compound of formula (XIV) wherein R³, R⁸, R⁶, R⁷ and R⁸ are hereinbefore defined and Z¹ is a suitable amine protecting group, with a compound of formula (XV) wherein R¹ and R⁹ are hereinbefore defined, a compound of formula (XVI) wherein R² is hereinbefore defined, and a compound of formula (IX) wherein R¹² represents alkyl, aralkyl, aryl, fused arylcycloalkyl, fused arylheterocyclyl, cycloalkyl, heteroaralkyl, heteroaryl, fused heteroarylcycloalkyl, fused heteroarylheterocyclyl, heterocyclyl; in a suitable solvent at about room temperature, to afford the intermediate compound (XVII), wherein R¹, R², R³, R⁸, R⁶, R⁷, R⁸, R⁹, R¹² and Z¹ are hereinbefore defined. The general reaction is illustrated in scheme 1 below:

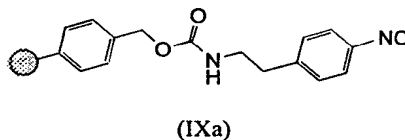


Scheme 1

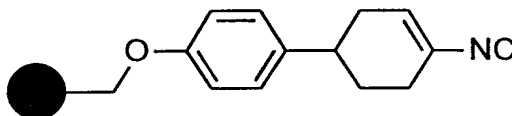
There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved (See Waki et al. J. Am. Chem. Soc., 1977, 6075-6077). Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene ; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers, such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl

phosphite, tetramethylsulphone, dimethyl sulphoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

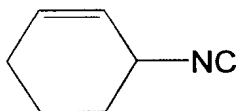
There is no restriction on the isonitrile (IX) used in the reaction scheme 1 above, provided that it has no adverse effect on the reaction involved. Examples of suitable isonitriles include, 1-isocyanocyclohexene, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide. Preferable isonitriles include the isonitrile functionalized polymer resin (IXa) or (XVIII), 1-isocyanocyclohexene (IXb), benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate. More preferably, isonitriles used in the reaction are isonitrile functionalized polymer resin (IXa)



or the isonitrile functionalized polymer resin (XVIII) (A. Piscopio, ORG Poster 232, American Chemical Society Meeting, Las Vegas, NV, 7-10 Sept., 1997):



or 1-isocyanocyclohexene (IXb):



The use of resin bound isonitriles (IXa) or (XVIII) in the synthesis of compounds of the formula (I), (II), (III) or (V), is advantageous over other non-resin bound isonitriles. The use of the resin bound isonitriles allow excess amount of reagents to be used in the reaction to drive the Ugi reaction forward. Also, unlike solution phase procedures, these reagents can be easily removed by subsequent washing of the resin, leaving the Ugi product clean and resin bound

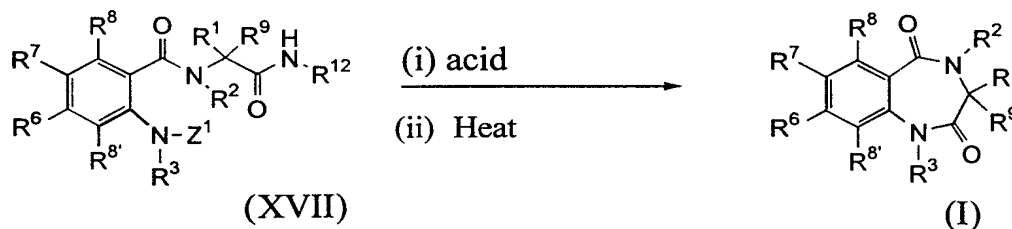
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely,

57

depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

The intermediate compound of the formula (XVII) thus prepared may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent in vacuo from the reaction mixture or, if necessary after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further purified by various well techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography. The intermediate compound is preferably recovered from the reaction mixture by distilling off the solvent in vacuo.

The intermediate compound (XVII) may be converted to a compound of formula (I) by reacting with acid and optionally base, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group (Z^1), followed by cyclization. This reaction is illustrated in Scheme 2.



Scheme 2

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 2 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate

removal of a base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

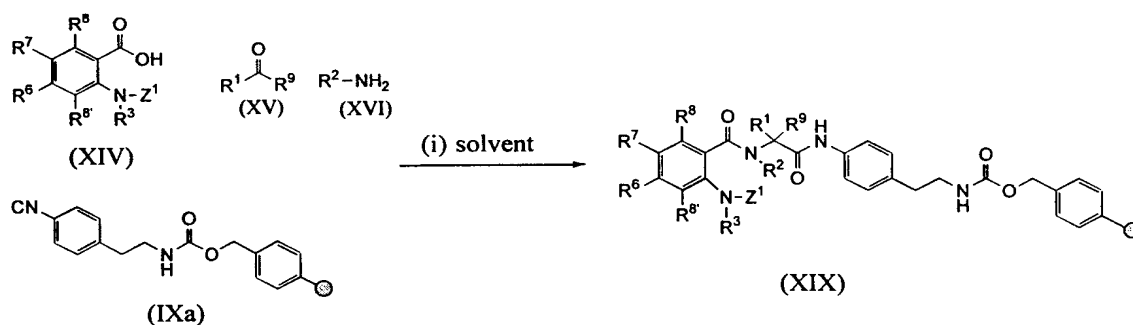
5 In situations where acidic conditions are used to remove the amine protecting group in (XVII) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its
10 corresponding free base form may be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction
15 temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3
20 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amino acid protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine
25 protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

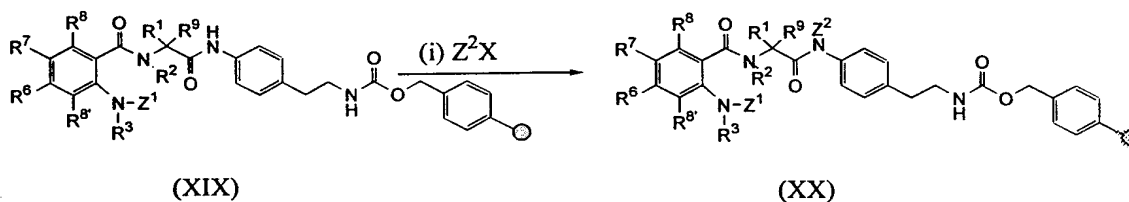
30 The use of the novel resin bound isonitrile (IXa) in the synthesis of compounds of the formula (I), wherein R^{12} is the novel resin bound isonitrile derivative (IXa), is advantageous over other non-resin bound isonitriles. However, use of (IXa) in the synthesis of (I) involves activation of the resin linker to facilitate cleavage of the resin linkage and cyclization to afford (I). An illustration of the use of the novel resin bound isonitrile (IXa) in the synthesis of the intermediate formula (XIX) is illustrated in
35 Scheme 3.

59



Scheme 3

Activation of the benzamide carbonyl of (XIX) to give the intermediate (XX), wherein Z² is a carbamate protective group promotes facile cleavage from the resin. Examples of carbamate protective groups which may activate the benzamide group, provided that they no adverse effect on the reaction involved are, for example, t-butyl-O-CO- (BOC), benzyl-O-CO- (CBZ), Cl₃CCH₂-O-CO- (Troc), (CH₃)₃SiCH₂CH₂-O-CO- (TEOC), 1-methyl-1-(4-biphenyl)ethyl-O-CO- (BPOC) and cycloalkyl-O-CO-. Other carbamate protective groups include those described in 'Protecting groups in Organic Synthesis' Greene, 1981, p. 223-49. An example of the activation of the benzamide group is illustrated in Scheme 4, wherein Z²X a suitable carbamate protective group reagent, for example (BOC)₂O.

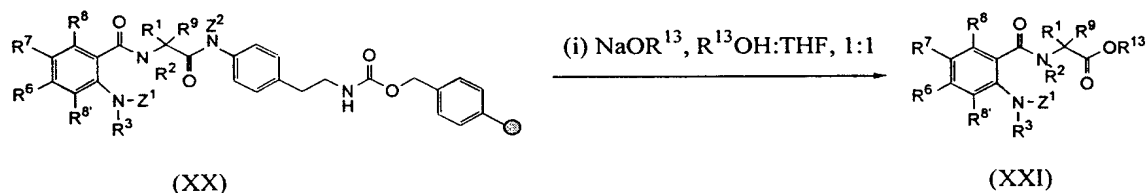


Scheme 4

The reaction conditions and reagents used in the activation of the benzamide, are ones that are known in the art of for the conversion of an amine to a carbamate group. This sort of reaction is usually carried out in dichloromethane, in the presence of a base, for example Et₃N, and a catalytic amount of DMAP. (For other reaction conditions, see 'Protecting groups in Organic Synthesis' Greene, 1981, p. 223-49).

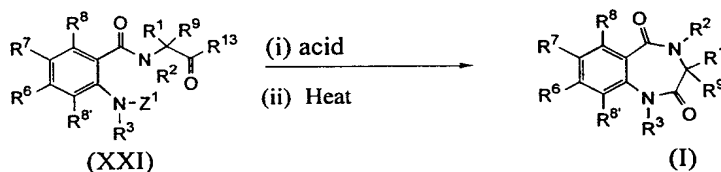
The resin "safety catch" linker is then cleaved, to facilitate the removal of the resin, by reacting the activated benzamide compound (XX) with an appropriate alkoxide, or hydroxide, to afford the corresponding alkyl ester or carboxylic acid derivative (XXI) respectively, wherein R¹³ is, for example, H, alkyl, phenyl or cycloalkyl (Mjalli, A.M.M., Sarshar, S., Baiga, T.J. *Tetrahedron Lett.* 1996, 37, 2943; Flynn, D. L., Zelle, R. E., Grieco, P. A. *J. Org. Chem.* 1983, 48, 2424.). An example of the cleavage from the resin is illustrated in reaction Scheme 5:

60



Scheme 5

The intermediate compound (XXI) may be converted to a compound of formula (I) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group (Z^1), followed by cyclization. This reaction is illustrated in Scheme 6.



Scheme 6

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 6 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However,

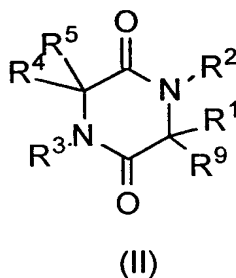
provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amino acid protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting groups include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting groups include 9-fluorenylmethyl carbamate (Fmoc).

In situations where acidic conditions are used to remove the amine protecting group in (XXI) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

Similarly, solid phase synthesis of a compound of formula (I) can be carried out using the resin bound isonitrile of formula (XVIII) using reaction conditions similar to those described for scheme 1 and scheme 2.

General methodology for the preparation of diketopiperazines (II)

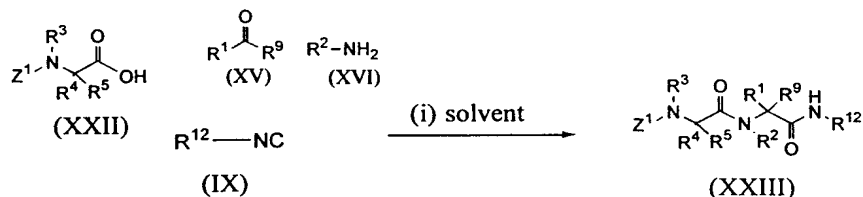


Compounds of formula II may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

In general terms, compounds of formula (II) wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^9 are hereinbefore defined and Z^1 is a suitable amine protecting group, may be synthesized by reacting an amino acid of

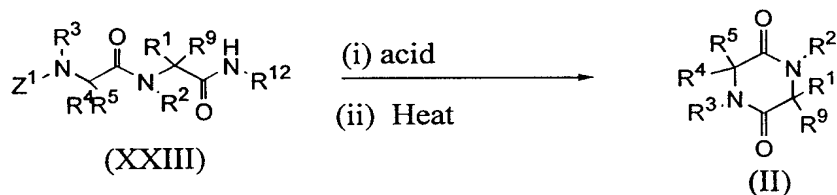
62

formula (XXII), wherein R^3 , R^4 , R^5 and Z^1 are hereinbefore defined, with compounds of formula (XV) wherein R^1 and R^9 are hereinbefore defined, (XVI) wherein R^2 is hereinbefore defined, and (IX) wherein R^{12} is hereinbefore defined, in a suitable solvent at about room temperature, to afford the intermediate compound (XXIII). This reaction is illustrated in Scheme 7 below:



The reaction conditions used for the synthesis of (XXIII), illustrated in Scheme 7, are similar to those described for the synthesis of (XVII) illustrated in Scheme 1.

The intermediate compound (XXIII) may be converted to a compound of formula (II) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group (Z^1), followed by cyclization. This reaction is illustrated in Scheme 8 below.



This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 8 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no

adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

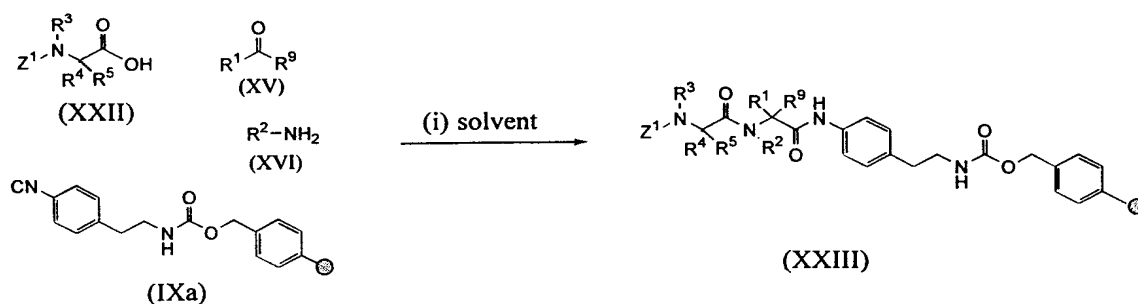
5 This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3
10 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine
15 protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

20 In situations where acidic conditions are used to remove the amine protecting group in (XXII) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of
25 the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

30 The use of the novel resin bound isonitrile (IXa) in the synthesis of compounds of the formula (XXII), wherein R^{12} is the novel resin bound isonitrile derivative, is advantageous over other non-resin bound isonitriles. However, use of (IXa) in the synthesis of (II) involves activation of the resin linker to facilitate cleavage of the resin linkage and cyclization to afford (II). An illustration of the use of the novel resin bound isonitrile (IXa) in the synthesis of the intermediate of the formula (XXIII) is illustrated in Scheme 9.

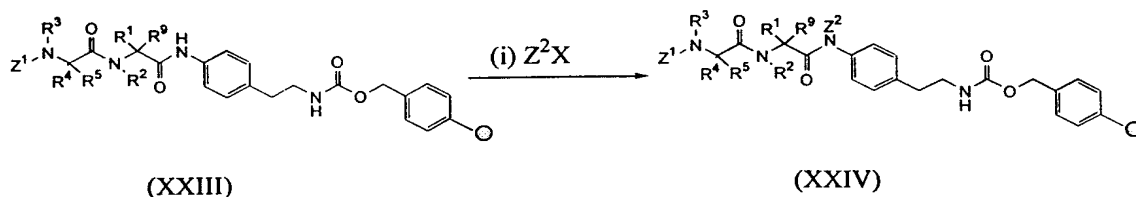
64



Scheme 9

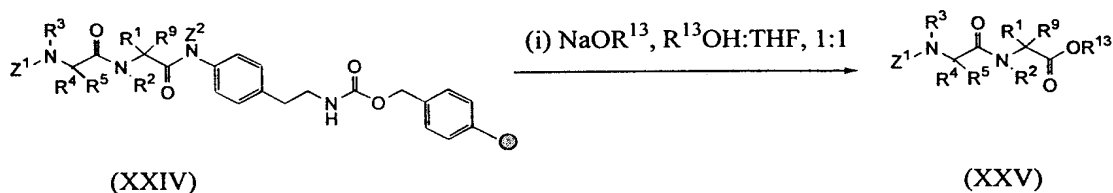
The reaction conditions, and isolation of the product, of the reaction illustrated in Scheme 9 are similar to those described for the synthesis of compound (XIX) illustrated in Scheme 3 above.

The benzamide compound (XXIII) is then activated for nucleophilic cleavage by conversion to intermediate (XXIV) under similar conditions to that described for synthesis of the intermediate (XX). The conversion of (XXIII) to (XXIV) is illustrated in Scheme 10.



Scheme 10

The resin "safety catch" linker is then cleaved, to facilitate the removal of the resin, by reacting the activated benzamide compound (XXIV) with an appropriate alkoxide, or hydroxide, affording the corresponding alkyl esters or carboxylic acids derivative (XXV) respectively, wherein R¹³ is, for example, H, alkyl, phenyl or cycloalkyl (Mjalli, A.M.M., Sarshar, S., Baiga, T.J. *Tetrahedron Lett.* 1996, 37, 2943; Flynn, D. L., Zelle, R. E., Grieco, P. A. *J. Org. Chem.* 1983, 48, 2424). An example of the cleavage from the resin is illustrated in reaction Scheme 11:

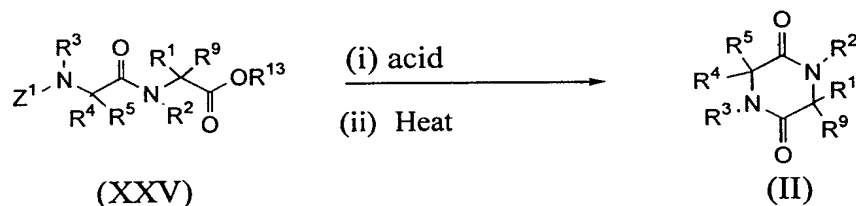


Scheme 11

The intermediate compound (XXV), may be converted to a compound of formula (II) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting

65

group (Z^1) and, wherein R^3 is an amine protecting group, removal of this amine protecting group also. The deprotected intermediate is then cyclized. This reaction is illustrated in Scheme 12.

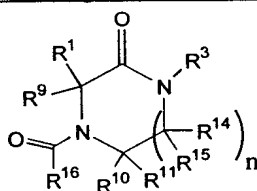


Scheme 12

The reaction conditions and reagents used for the synthesis of (II), illustrated in Scheme 12, are similar to those described for the synthesis of (I) illustrated in Scheme 6.

In situations where acidic conditions are used to remove the amine protecting group in (XXV) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

General methodology for the preparation of ketopiperazines and dihydroquinoxalinones derivatives of general formula (III):-.



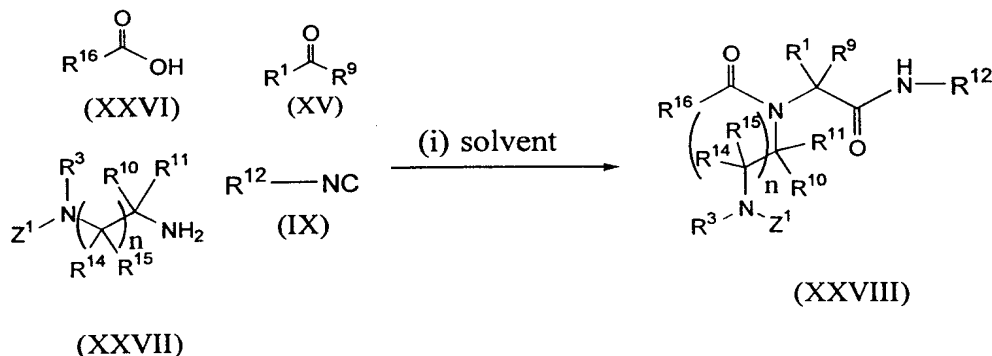
(III)

Compounds of formula (III) may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

In general terms, compounds of formula (III) wherein n , R^1 , R^3 , R^9 , R^{10} , R^{11} , R^{14} , R^{15} and R^{16} are hereinbefore defined, may be synthesized via a '3-step, 1-pot' procedure by reacting a compound of formula (XXVI) wherein R^{16} is hereinbefore defined, with a compound of formula (XXVII) wherein n , R^3 , R^{10} , R^{11} , R^{14} and R^{15} are hereinbefore defined and Z^1 is a suitable amine protecting group, (XV)

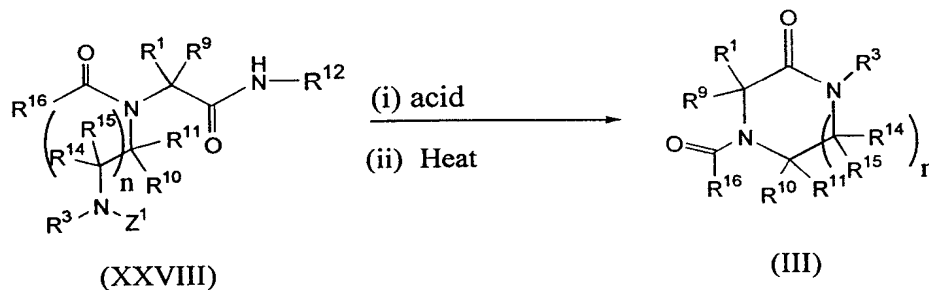
66

wherein R^1 and R^9 are hereinbefore defined, and (IX) wherein R^{12} is hereinbefore defined, in a suitable solvent at about room temperature, to afford the intermediate compound (XXVIII), wherein n , R^1 , R^3 , R^9 , R^{10} , R^{11} , R^{12} , R^{14} , R^{15} , R^{16} and Z^1 are hereinbefore defined. The general reaction is illustrated in Scheme 13 below:



10 The reaction conditions used for the synthesis of (XVIII), illustrated in Scheme 13, are similar to those described for the synthesis of (XVII) illustrated in Scheme 1.

The intermediate compound (XXVIII) may be converted to a compound of formula (III) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group (Z^1), followed by cyclization. This reaction is illustrated in Scheme 14 below.



This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 14 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z¹, wherein Z¹ is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate
5 removal of an base labile amine protecting group Z¹, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction
10 temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3
15 hours to 36 hours will usually suffice.

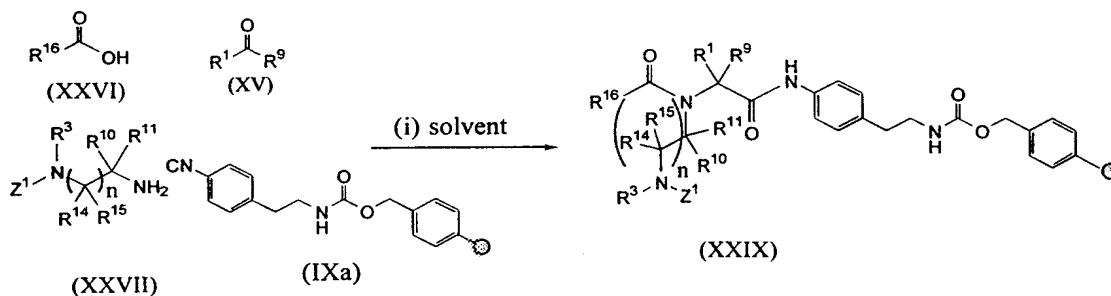
There is no particular restriction on the amine protecting group (Z¹) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine
20 protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

In situations where acidic conditions are used to remove the amine protecting group in (XXVIII) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of
30 the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

The use of the novel resin bound isonitrile (IXa) in the synthesis of compounds of the formula
35 (XXVIII) wherein R¹² novel resin bound isonitrile derivative is advantageous over other non-resin bound isonitriles. However, use of (IXa) in the synthesis of (III) involves activation of the resin linker to facilitate cleavage of the resin linkage and cyclization to afford (III). An illustration of the use of the

68

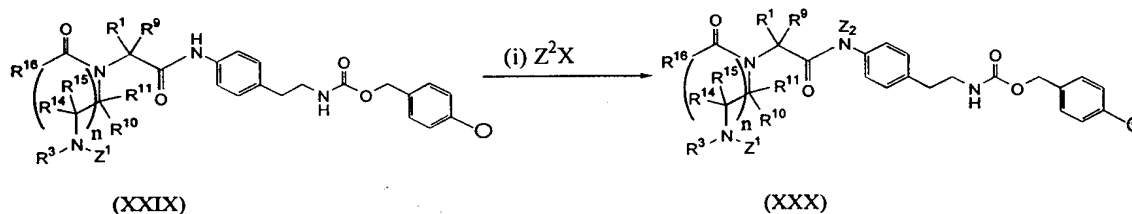
novel resin bound isonitrile (IXa) in the synthesis of the intermediate of the formula (XXIX) is illustrated in Scheme 15 below.



Scheme 15

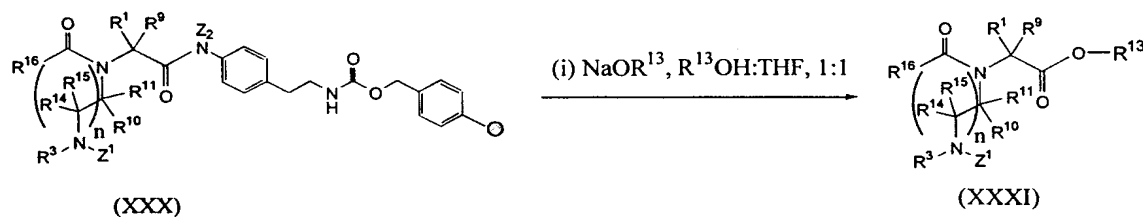
The reaction conditions, and isolation of the product, of the reaction illustrated in Scheme 15 are similar to those described for the synthesis of compound (XIX) illustrated in Scheme 3 above.

The benzamide compound (XXIX) is then activated for nucleophilic cleavage by conversion to intermediate (XXX) under similar conditions to that described for synthesis of the intermediate (XX). The conversion of (XXIX) to (XXX) is illustrated in Scheme 16.



Scheme 16

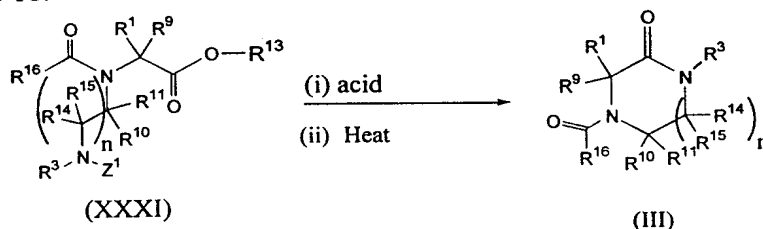
The resin "safety catch" linker is then cleaved, to facilitate the removal of the resin, by reacting the activated benzamide compound (XXX) with an appropriate alkoxide, or hydroxide, affording the corresponding alkyl esters or carboxylic acids derivative (XXXI) respectively, by the same procedure as described for the synthesis of (XXV) above. An illustration of the cleavage from the resin is illustrated in reaction Scheme 17:



69

Scheme 17

The intermediate compound (XXXI), may be converted to a compound of formula (III) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group (Z^1) and, wherein R^3 is an amine protecting group, removal of this amine protecting group also. The deprotected intermediate is then cyclized to afford the product (III). This reaction is illustrated in Scheme 18.



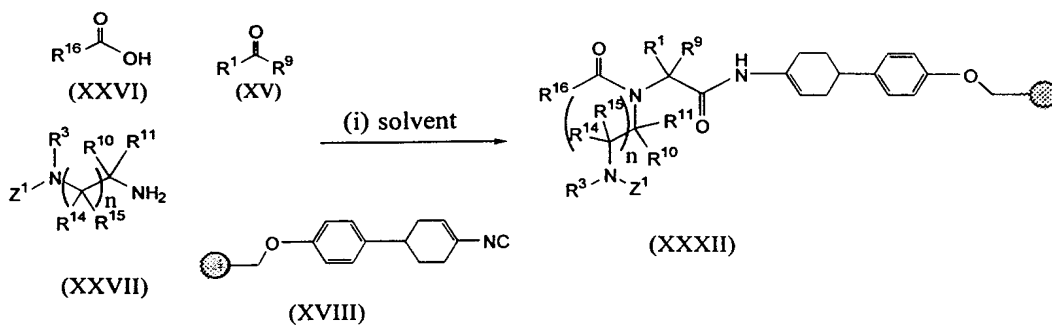
Scheme 15

The reaction conditions and reagents used for the synthesis of (III), illustrated in Scheme 18, are similar to those described for the synthesis of (I) illustrated in Scheme 6.

In situations where acidic conditions are used to remove the amine protecting group in (XXXI) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

The use of the resin bound isonitrile (XVIII) in the synthesis of compounds of the formula (XXVIII), wherein R^{12} is the resin bound isonitrile derivative (XVIII), is advantageous over other non-resin bound isonitriles. However, use of (IXa) in the synthesis of (III) involves activation of the resin linker to facilitate cleavage of the resin linkage and cyclization to afford (III). An illustration of the use of the novel resin bound isonitrile (XVIII) in the synthesis of the intermediate of the formula (XXXII) is illustrated in Scheme 19.

70



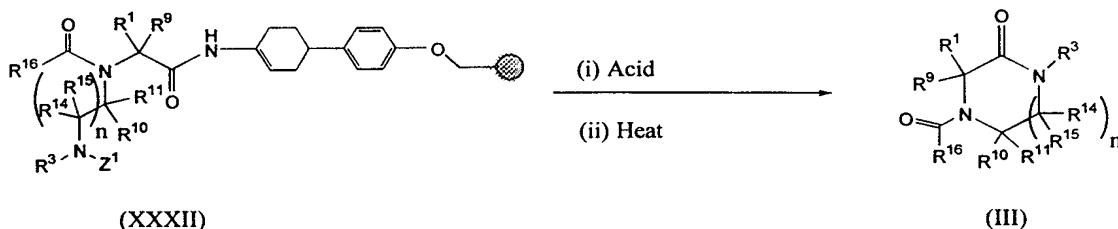
Scheme 19

The reaction conditions used for the synthesis of (XXXII), illustrated in Scheme 19, are similar to those described for the synthesis of (XVII) illustrated in Scheme 1.

5

The intermediate compound (XXXII) may be converted to a compound of formula (III) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in Scheme 20.

10



Scheme 20

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

20

In addition to carrying out the reaction in scheme 20 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

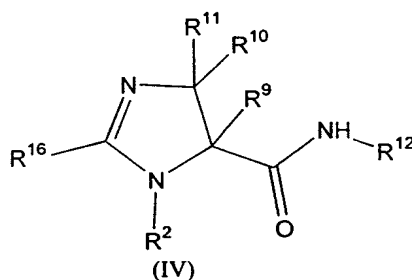
25

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting groups include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting groups include 9-fluorenylmethyl carbamate (FMOC).

In situations where acidic conditions are used to remove the amine protecting group in (XXXII) it may also be necessary to treat the deprotected intermediate, which is present as an acid salt, with base so as to convert the acid addition salt to its corresponding free base. There is no particular restriction on the nature of the base to be used. A base conventionally used to convert an acid addition salt to its corresponding free base form may be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include ammonia, piperidine, morpholine, ethanolamine, diethylamine, polystyrene bound di-isopropylethylamine or basic DOWEX. Preferably diethylamine, basic DOWEX or polystyrene bound di-isopropylethylamine.

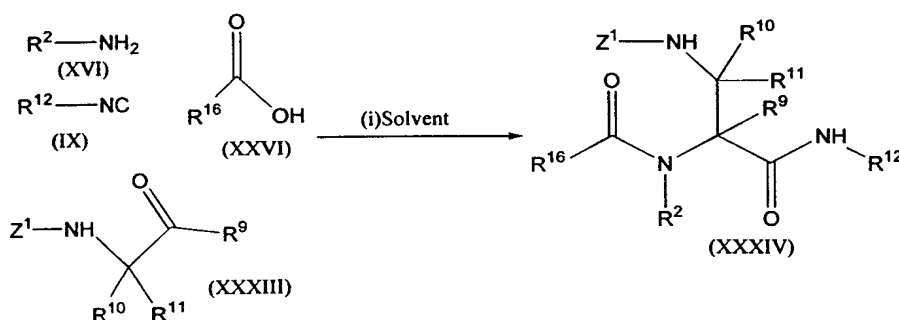
General methodology for the preparation of
dihydroimidazole derivatives of general formula (IV)



In general terms, compounds of formula (IV) wherein R^2 , R^9 , R^{10} , R^{11} , R^{12} and R^{16} are hereinbefore defined, may be synthesized via a '3-step, 1-pot' procedure by reacting a compound of

formula (XXVI) wherein R^{16} is hereinbefore defined with compound of formula (XXXIII) wherein R^9 , R^{10} and R^{11} are hereinbefore defined and Z^1 is a amine protecting group, (IX) wherein R^{12} is hereinbefore defined, and (XVI) wherein R^2 is hereinbefore defined, in a suitable solvent at about room temperature, to afford the intermediate compound (XXXIV), wherein R^2 , R^9 , R^{10} , R^{11} , R^{12} , Z^1 and R^{16} , are

5 hereinbefore. The general reaction is illustrated in scheme 21 below:



Scheme 21

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved (See Waki et al. J. Am. Chem. Soc., 1977, 6075-6077). Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene ; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers, such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethylsulphone, dimethyl sulfoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

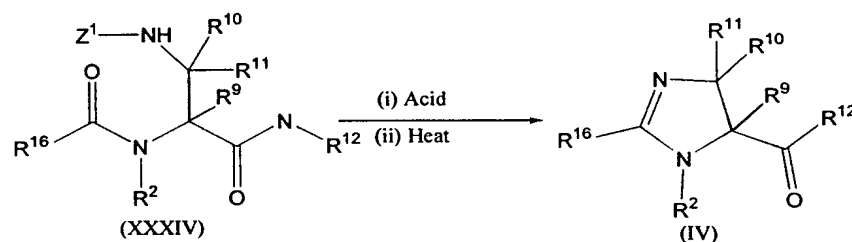
There is no restriction on the isocyanide used in the reaction scheme 21 above. Examples of suitable isocyanides include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide. Preferable isocyanides include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C , preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

73

The intermediate compound of the formula (XXXIV) thus prepared may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent in vacuo from the reaction mixture or, if necessary after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further purified by various well techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography. The intermediate compound is preferably recovered from the reaction mixture by distilling off the solvent in vacuo.

The intermediate compound (XXXIV) may be converted to a compound of formula (IV) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 22.



Scheme 22

Cyclization of the deprotected amine to dihydroimidazole proceeded an average of 66% of possible dihydroimidazole product. The remaining no-cyclized amines are removed via a solution phase scavenging step with the simultaneous addition of PS-DIEA or PS-tris(2-aminoethyl)amine (6 equiv.) and PS-NCO (3 equiv.) in dichloroethane. (Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* 1997, 119, 4882. Flynn, D.L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodward, S. *J. Am. Chem. Soc.* 1997, 119, 4874. Purchased from Argonaut[®] technologies (PS-DIEA - polystyrene bound diisopropylethylamine)).

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z¹ and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

74

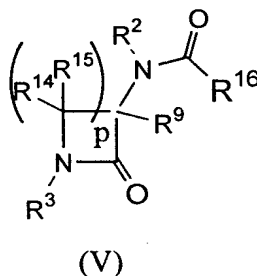
In addition to carrying out the reaction in scheme 22 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C , preferably from room temperature to about 100°C , more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, acid labile amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC).

It is also envisaged that a solid phase synthesis of (IV) could be carried out using a resin bound Ugi component (XII), (IXa), (XV) or (XXXIII) using similar reaction conditions as described herein.

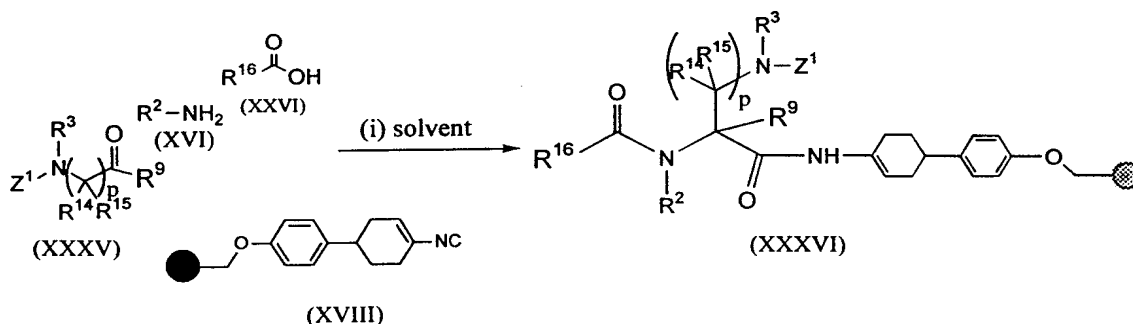
General methodology for the preparation of
lactam derivatives of general formula (V)



In general terms, compounds of formula (V) wherein p , R^1 , R^2 , R^3 , R^9 , R^{14} , R^{15} and R^{16} are hereinbefore defined, may be synthesized via a '3-step, 1-pot' procedure by reacting a compound of

75

formula (XXVI) wherein R^{16} is hereinbefore defined, with a compound of formula (XXXV) wherein p , R^3 , R^9 , R^{14} , R^{15} and Z^1 are hereinbefore defined, (XVI) wherein R^2 is as hereinbefore defined, and (XVIII) in a suitable solvent at about room temperature, to afford the intermediate compound (XXXVI), wherein p , R^3 , R^9 , R^{14} , R^{15} , R^{16} and Z^1 are as hereinbefore defined. The general reaction is illustrated in Scheme 23 below:



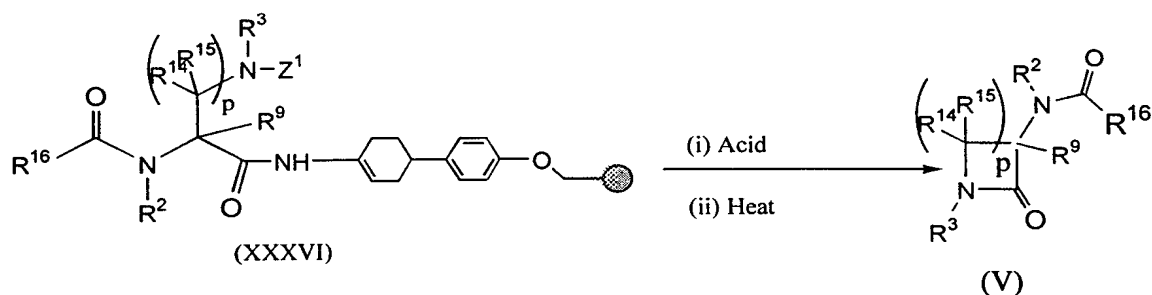
Scheme 23

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved (See Waki et al. J. Am. Chem. Soc., 1977, 6075-6077). Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers, such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethylsulphone, dimethyl sulphoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

The intermediate compound (XXXVI) may be converted to a compound of formula (V) by reacting with acid or base, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 24 below:

76



Scheme 24

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C , preferably from room temperature to about 100°C , more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

Similarly, the synthesis of (V) can be carried out in solid phase using an isonitrile bound resin of formula (IXa) and using reaction conditions similar to those described for schemes 15-18.

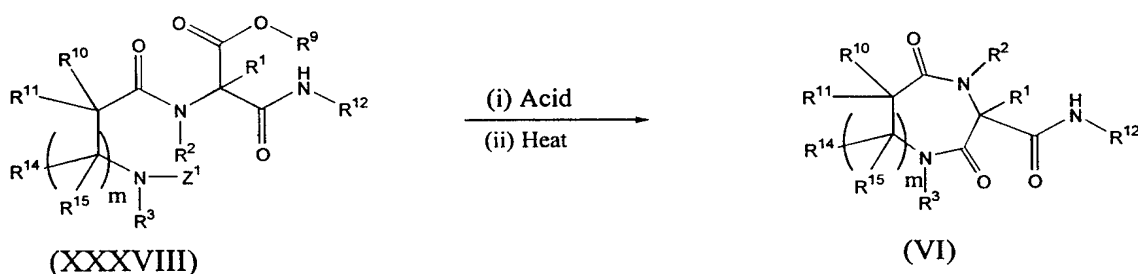
Similarly, the synthesis of (V) can be carried out in solution phase using a non resin bound isonitrile.

There is no restriction on the isonitrile ($R^{12}-NC$) used in the reaction scheme above, provided that it has no adverse effect on the reaction involved. Examples of suitable isonitriles include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide. Preferable isocyanides include cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about $0^{\circ}C$ to about $150^{\circ}C$, preferably from room temperature to about $100^{\circ}C$, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

The intermediate compound of the formula (XXXVIII) thus prepared may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent in vacuo from the reaction mixture or, if necessary after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further purified by various well techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography. The intermediate compound is preferably recovered from the reaction mixture by distilling off the solvent in vacuo.

The intermediate compound (XXXVIII) may be converted to a compound of formula (VI) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 26.



Scheme 26

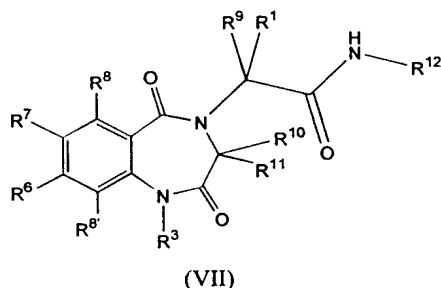
This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z¹ and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 26 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z¹, wherein Z¹ is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z¹, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z¹) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

General methodology for the preparation of 1,4-benzodiazepine-2,5-dione derivatives of general formula (VII)



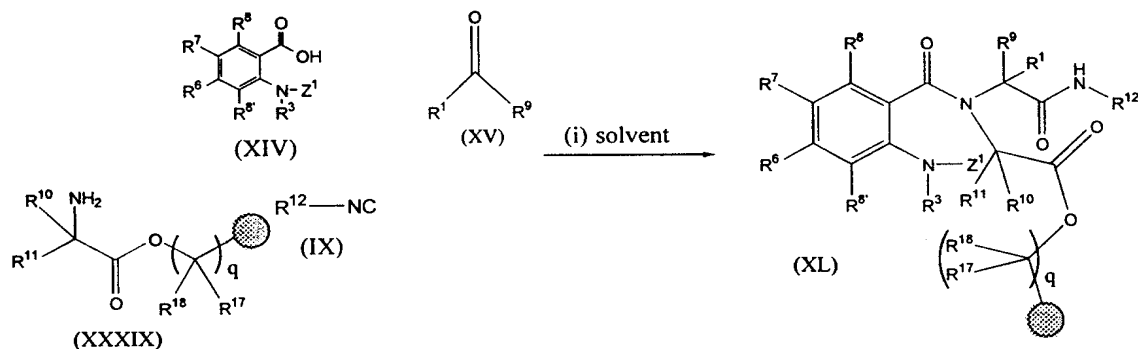
5

Compounds of formula (VII) may be prepared may be synthesized via a '3-step, 1-pot' procedure by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

10

In general terms, compounds of formula (VII) wherein R¹, R³, R⁸, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are hereinbefore defined, and Z¹ is a suitable amine protecting group, may be synthesized by reacting an isonitrile compound of formula (IX), wherein R¹², is hereinbefore defined, with compounds of formula (XV) wherein R¹ and R⁹ are hereinbefore defined, (XIV) wherein R³, R⁸, R⁶, R⁷ and R⁸ are hereinbefore defined and amino ester bound resin compound (XXXIX) wherein R¹⁰, R¹¹ are as hereinbefore defined, R¹⁷ and R¹⁸ independently represent hydrogen, alkyl, aralkyl, aryl, fused arylcycloalkyl, fused arylheterocyclyl, aryloxy, cycloalkyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclyl, or heterocyclyl, most preferably, alkyl or hydrogen; and q is 1, 2 or 3, in a suitable solvent at about room temperature, to afford the intermediate compound (XL). This reaction is illustrated in scheme 27 below:

20



Scheme 27

There is no restriction on the isonitrile used in the reaction scheme 27 above. Examples of suitable isonitriles include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and

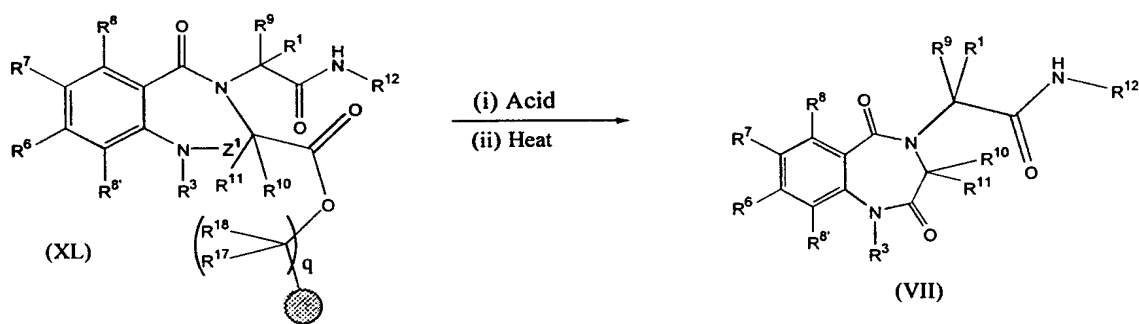
25

1,1,3,3-tetramethylbutyl isocyanide. Preferable isonitriles include benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate. More preferably 1-isocyanocyclohexene.

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers, such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethylsulphone, dimethyl sulphoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

The intermediate compound (XL) may be converted to a compound of formula (VII) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 28 below:



Scheme 28

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z¹ and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the

reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

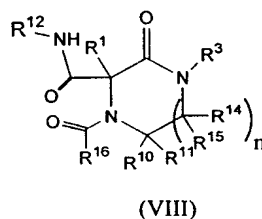
In addition to carrying out the reaction in scheme 28 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

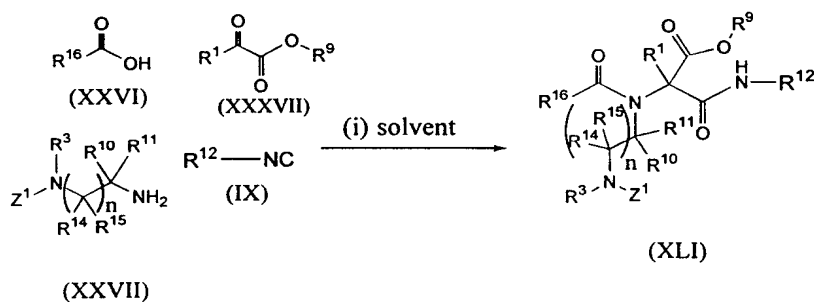
There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (Fmoc).

Similarly, the synthesis of (VII) can be carried out in solution phase using a non resin bound amino ester.

General methodology for the preparation of Ketopiperazine and Dihydroquinoxalinone derivatives of general formula (VIII)



In general terms, compounds of formula (VIII) wherein n , R^1 , R^3 , R^{10} , R^{11} , R^{12} , R^{14} , R^{15} and R^{16} are hereinbefore defined, may be synthesized via a '3-step, 1-pot' procedure by reacting a compound of formula (XXVI) wherein R^{16} is hereinbefore defined, with a compound of formula (XXVII) wherein n , R^3 , R^{10} , R^{11} , R^{14} and R^{15} are hereinbefore defined and Z^1 is a suitable amine protecting group, (XXXVII) wherein R^1 and R^9 are hereinbefore defined, and (IX) wherein R^{12} is hereinbefore defined, in a suitable solvent at about room temperature, to afford the intermediate compound (XLI), wherein n , R^1 , R^3 , R^9 , R^{10} , R^{11} , R^{14} , R^{15} , R^{16} and Z^1 are hereinbefore defined. The general reaction is illustrated in Scheme 29 below:



Scheme 29

It is known that when the nucleophilicity of the nitrogen atom adjacent to R^{10} and R^{11} is poor, the Passerini reaction (See J. March, Advanced Organic Chemistry, 3rd Ed., John Wiley & Sons p. 870-871 (1985)) predominates and the yields of the desired cyclized product (VIII) is lowered. Therefore, it is preferred that at least one of R^{10} or R^{11} , is an electron donating group, or when $n=1$, R^{11} and R^{14} are absent and R^{10} and R^{15} taken together with the adjacent carbon atoms through which they are linked form an electron donating 6 membered aryl or 5 to 6 membered an electron donating heteroaryl; or when $n=1$, R^{10} and R^{15} taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered an electron donating cycloalkyl or an electron donating heterocyclyl; or when $n=2$, adjacent R^{11} and R^{14} are absent and R^{10} and adjacent R^{15} taken together with the adjacent carbon atoms through which they are linked form a 6 membered an electron donating aryl or 5 to 6 membered an electron donating heteroaryl; or when $n=2$, R^{10} and adjacent R^{15} taken together with the adjacent carbon atoms through which they are linked form a 5 to 7 membered an electron donating cycloalkyl or an electron donating heterocyclyl; so as to increase the nucleophilicity of the adjacent nitrogen atom and give higher yields of the desired product (VIII).

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved (See Waki et al. J. Am. Chem. Soc., 1977, 6075-6077). Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers,

84

such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethylsulphone, dimethyl sulphoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

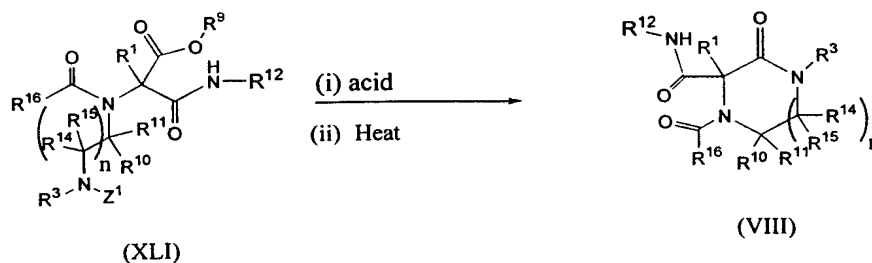
5 There is no restriction on the isonitrile (R^{12} -NC) used in the reaction scheme above, provided that it has no adverse effect on the reaction involved. Examples of suitable isonitriles include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide. Preferable isonitriles include cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide,
10 isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide.

 The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more
15 preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

20 The intermediate compound of the formula (XLI) thus prepared may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent in vacuo from the reaction mixture or, if necessary after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further
25 purified by various well techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography. The intermediate compound is preferably recovered from the reaction mixture by distilling off the solvent in vacuo.

30 The intermediate compound (XLI) may be converted to a compound of formula (VIII) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 30.

85



Scheme 30

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z^1 and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

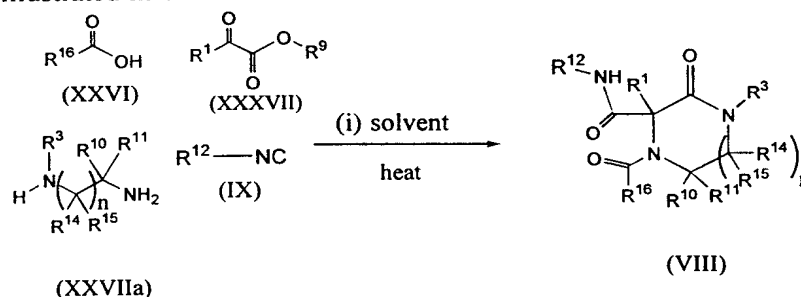
In addition to carrying out the reaction in scheme 30 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z^1 , wherein Z^1 is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z^1 , may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C , preferably from room temperature to about 100°C , more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting group include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-

isopropoxy carbonyl (BPOC). Preferred base labile amine protecting group include 9-fluorenylmethyl carbamate (FMOC).

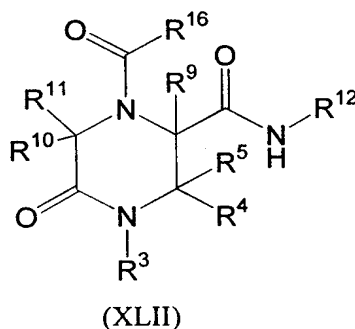
Alternatively, a compound of the formula (VIII) wherein n , R^1 , R^{10} , R^{11} , R^{12} , R^{14} , R^{15} and R^{16} are
 5 hereinbefore defined and R^3 is hydrogen, may be prepared by '2-step, one pot' method by reacting a compound of formula (XXVI) wherein R^{16} is hereinbefore defined, with a compound of formula (XXVIIa) wherein n , R^{10} , R^{11} , R^{14} and R^{15} are hereinbefore defined and R^3 is hydrogen, (XXXVII) wherein R^1 and R^9 are hereinbefore defined, and (IX) wherein R^{12} is hereinbefore defined, in a suitable solvent and appropriate temperature to effect cyclization and afford a compound of formula (VIII). The
 10 general reaction is illustrated in Scheme 31 below:



Scheme 31

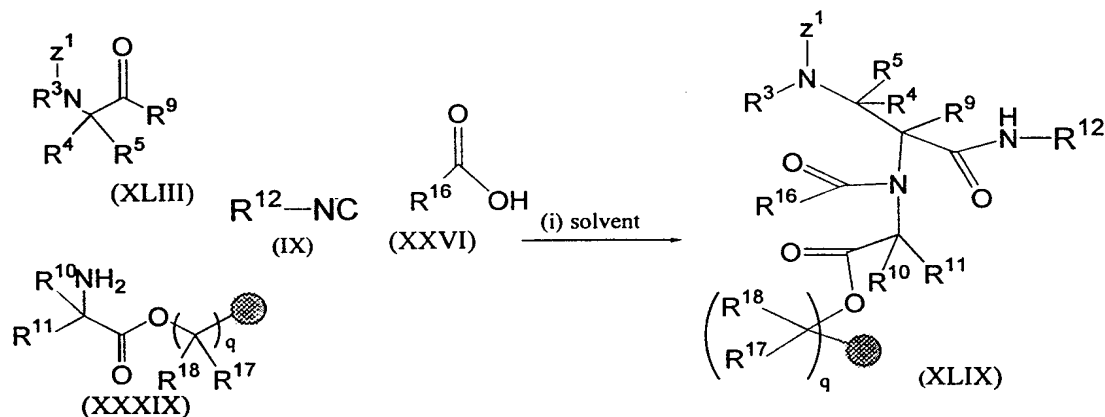
The solvent and isonitrile used in this reaction are similar to those used for the synthesis of (XLI) illustrated in Scheme 30. The reaction temperature used in this reaction is similar to that used for the
 15 cyclization of (XLI) illustrated in Scheme 30. It would also be understood by a skilled person in the art that use of a diamino compound of formula (XXVIIa) wherein R^{10} , R^{11} , R^{14} and R^{15} are identical to each other would produce a single compound of formula (VIII).

General methodology for the preparation of ketopiperazine derivatives of general formula (XLII)



Compounds of formula (XLII) may be prepared may be synthesized via a '3-step, 1-pot'
 25 procedure by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

In general terms, compounds of formula (XLII) wherein R^3 , R^4 , R^5 , R^9 , R^{10} , R^{11} , R^{12} and R^{16} , are hereinbefore defined, may be synthesized by reacting an isonitrile compound of formula (IX), wherein R^{12} , is hereinbefore defined, with compounds of formula (XLIII) wherein R^3 , R^4 , R^5 , R^9 and Z^1 are hereinbefore defined, (XXVI) wherein R^{16} is hereinbefore defined and amino ester bound resin compound (XXXIX) wherein R^{10} , R^{11} are as hereinbefore defined, R^{17} and R^{18} independently represent hydrogen, alkoxy carbonyl, alkyl, aralkoxy carbonyl, aralkyl, aroyl, aryl, fused arylcycloalkyl, fused arylheterocyclyl, aryloxy, aryloxy carbonyl, cycloalkyl, heteroaralkyl, heteroaroyl, heteroaryl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclyl, or heterocyclyl; and q is 1, 2 or 3, in a suitable solvent at about room temperature, to afford the intermediate compound (XLIX). This reaction is illustrated in scheme 29 below:



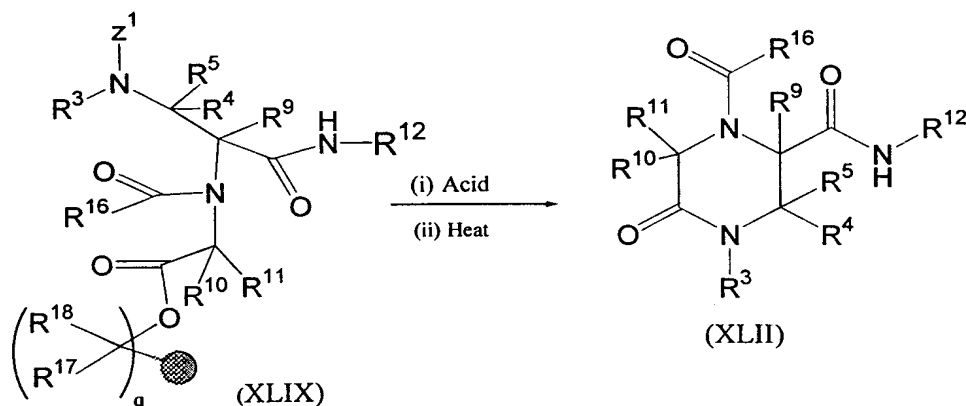
Scheme 32

There is no restriction on the isonitrile used in the reaction scheme 29 above. Examples of suitable isonitriles include, benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate, cyclohexyl isocyanide, 2,6-dimethylphenyl isocyanide, methyl isocyanoacetate, isopropyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide. Preferable isonitriles include benzyl isocyanide, n-butyl isocyanide, diethyl isocyanomethyl phosphonate. More preferably 1-isocyanocyclohexene.

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: alcohols, such as methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol; hydrocarbons, such as benzene and toluene; amides, such as dimethyl acetamide, dimethylformamide; halides, such as dichloromethane, dichloroethane; and ethers, such as tetrahydrofuran and dioxane; other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethylsulphone, dimethyl sulphoxide, acetonitrile and pyridine. Of these solvents, the alcohols are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

The intermediate compound (XLIX) may be converted to a compound of formula (XLII) by reacting with acid, in a suitable solvent and appropriate temperature, to effect removal of the amine protecting group, followed by cyclization. This reaction is illustrated in scheme 33 below:



Scheme 33

This reaction is carried out in the presence of an acid. There is no particular restriction on the nature of the acid to be used in this reaction, and any acid conventionally used to facilitate removal of an acid labile amine protecting group Z¹ and cyclization, may equally be used here, provided that it has no adverse effect on other parts of the molecule. Examples of suitable acids include: mineral acids such as hydrochloric acid or sulfuric acid; organic acids such as trifluoroacetic acid. Acids to be used in the reaction can also be generated in situ, for example by the addition of acetyl chloride in methanol, to generate hydrochloric acid. Preferably, anhydrous acids are used.

In addition to carrying out the reaction in scheme 29 in the presence of acid, a reaction step involving basic conditions can also be optionally carried out so as to facilitate the removal of the amine protecting group Z¹, wherein Z¹ is a base labile amine protecting group. There is no particular restriction on the nature of the base to be used in this reaction, and any base conventionally used to facilitate removal of an base labile amine protecting group Z¹, may equally be used here, provided that it has no

adverse effect on other parts of the molecule. Examples of suitable bases include: organic bases such as ammonia, piperidine, morpholine, ethanolamine and diethylamine.

This reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to 36 hours will usually suffice.

There is no particular restriction on the amine protecting group (Z^1) employed. However, amine protecting groups which allow removal of the protecting group and cyclization of the deprotected intermediate, without purification or isolation of intermediates, are preferred. Examples of amine protecting groups include both acid labile amine protecting groups and base labile protecting groups. Preferred acid labile amine protecting groups include *tert*-butoxycarbonyl (BOC) and 2-(4-biphenyl)-isopropoxy carbonyl (BPOC). Preferred base labile amine protecting groups include 9-fluorenylmethyl carbamate (FMOC).

Similarly, the synthesis of (XLII) can be carried out in solution phase using a non resin bound amino ester.

According to a further feature of the present invention, compounds of the invention may be prepared by interconversion of other compounds of the invention.

A compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (XLII), including a group containing one or more nitrogen ring atoms, preferably imine (=N-), may be converted to the corresponding compound wherein one or more nitrogen ring atom of the group is oxidized to an N-oxide, preferably by reacting with a peracid, for example peracetic acid in acetic acid or m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature.

As an example of the interconversion process, compounds (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (XLII), containing sulphoxide linkages may be prepared by the oxidation of corresponding compounds containing -S- linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperoxybenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH 5, at

temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, compounds (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (XLII), containing sulphone linkages may be prepared by the oxidation of corresponding compounds containing -S- or sulfoxide linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature.

It will be understood that designation of aromaticity with respect to carbocycles and heterocycles herein includes any highly resonant unsaturated ring structure. Alternatively, placement of double bonds, where indicated, represents one potential structure for the depicted compound but will be understood to include other resonant states of the compound as well as protonated and charged species, only one of which may be shown.

It will be appreciated that compounds of the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I), a compound of formula (II), or a compound of formula (III), hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates.

For the propose herein it is understood that tautermeric forms are included in the recitation of a given group, e.g., thio/mercapto or oxo/hydroxyl.

Acid additional salts are formed with the compounds of the invention in which a basic function such as an amino, alkylamino, or dialkylamino group is present. The pharmaceutically acceptable, i.e., nontoxic, acid addition salts are preferred. The salts chosen are chosen optimally to be compatible with the customary pharmaceutical vehicles and adapted for oral or parenteral administration. Acid addition salts of the compounds of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution. Some suitable acids for use in

the preparation of such salts are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, various organic carboxylic and sulfonic acids, such as acetic acid, citric acid, propionic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid, malic acid, methanesulfonic acid, toluenesulfonic acid, fatty acids, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, 5 cyclopentanepropionate, digluconate, dodecylsulfate, bisulfate, butyrate, lactate, laurate, lauryl sulfate, malate, hydroiodide, 2-hydroxy-ethanesulfonate, glycerophosphate, picrate, pivalate, pamoate, pectinate, persulfate, 3-phenylpropionate, thiocyanate, 2-naphthalenesulfonate, undecanoate, nicotinate, hemisulfate, heptonate, hexanoate, camphorate, camphersulfonate, and others.

10 The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

15 Compounds of this invention can be regenerated from their base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

20 Base addition salts may be formed where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including those derived from alkali and alkaline earth metal 25 salts, within the scope of the invention include those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, 30 tetramethylammonium hydroxide, and the like.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol.

35

EXAMPLE 1

Solution Phase Synthesis of Compounds of Formula (I) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

92

Equal amounts (0.1 ml) of 0.1 M solutions of the four appropriate components compound of formulae (XIV), (XV), (XVI) and (IXb), are employed generating a theoretical 10 μ mol of final 1,4-benzodiazepine-2,5-dione product (I) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane. Solvents are then evaporated at 65 °C to afford the cyclized product compound of formula (I). Lc/ms analysis (liquid chromatography/mass spectrometry) is performed using a C18 Hypersil BDS 3m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 15 min, at a rate of 1 ml/min. Desired products are seen as (M+ 1).

Table 5 below shows the lc/ms A% yields taken from two 96 well plates using the experimental procedure described above and the Ugi components listed as 1-22 below:

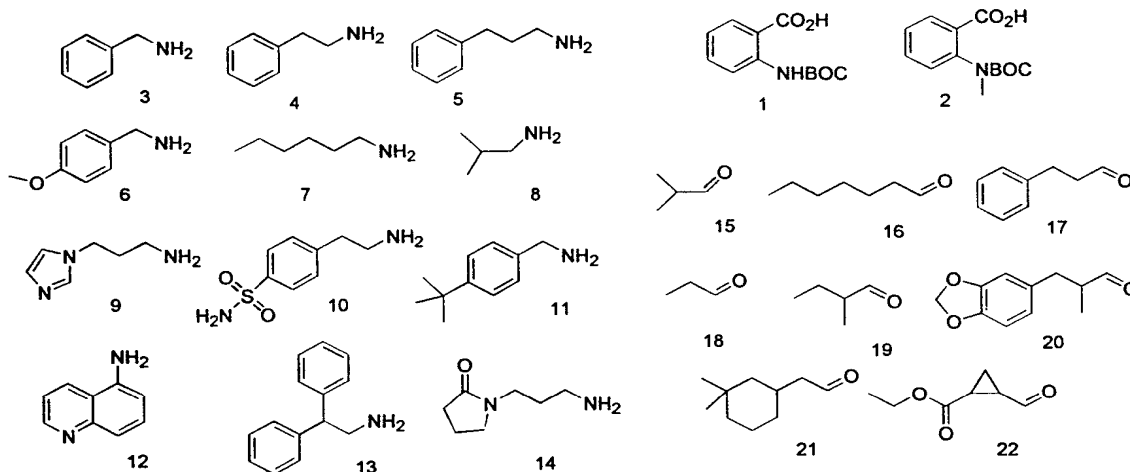


Table 1 contains hplc retention times of the desired products from anthranilic acid 1 using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA in H₂O/CH₃CN 10% to 100%, 5 min, at a rate of 1 ml/min. For example, Table 1 indicates that anthranilic acid 1 reacted with amine 3 and aldehyde 15 affords the desired product with a retention time of 3.78, under the conditions mentioned above.

93

TABLE 1

	3	4	5	6	7	8	9	10	11	12	13	14
15	3.78	3.92	4.18	3.79	3.52	4.14	2.82	3.26	4.63	2.86	4.36	3.04
16	4.71	4.84	5.15	4.67	4.58	4.97	3.70	4.14	5.46	3.61	5.15	4.01
17	4.31	4.40	4.67	4.27	4.14	4.58	3.35	3.79	5.02	3.30	4.75	3.61
18	3.61	3.79	4.05	3.65	3.35	4.01	2.55	3.04	4.53	2.46	4.27	2.82
19	4.01	4.14	4.01	4.01	3.83	4.36	3.04	3.48	4.80	4.58	3.26	4.27
20	4.27	4.40	4.62	4.27	4.14	4.53	3.04	3.83	4.97	3.43	4.75	3.65
21	5.11	5.20	5.50	5.02	4.97	5.33	4.05	4.49	5.86	3.92	5.55	4.36
22	3.43	3.74	3.91	3.48	3.34	3.87	2.64	3.08	4.31	2.95	4.18	2.86

Table 2 contains the molecular weight of the desired products from anthranilic acid 1. Desired products are seen as (M+ 1). For example, Table 2 indicates that anthranilic acid 1 reacted with amine 3 and aldehyde 15 affords the desired product with a molecule weight (M+1) of 308.4, under the conditions mentioned above.

TABLE 2

	3	4	5	6	7	8	9	10	11	12	13	14
15	308.4	322.4	302.4	338.4	274.4	336.4	326.4	401.5	364.5	345.4	398.5	343.4
16	350.5	364.5	344.5	380.5	316.4	378.5	368.5	443.6	406.6	387.5	440.6	385.5
17	370.5	384.5	364.5	400.5	336.4	398.5	388.5	463.6	426.6	407.5	460.6	405.5
18	294.4	308.4	288.4	324.4	260.3	322.4	312.4	387.5	350.5	331.4	384.5	329.4
19	322.4	336.4	316.4	352.4	288.4	350.5	340.4	415.5	378.5	359.4	412.5	357.5
20	428.5	442.5	422.5	458.5	394.5	456.5	446.5	521.6	484.6	465.5	518.6	463.5
21	390.5	404.6	384.6	420.6	356.5	418.6	408.5	483.6	446.6	427.6	480.7	425.6
22	378.4	392.5	372.5	408.5	344.4	406.5	396.4	471.5	434.5	415.5	468.6	413.5

Table 3 contains hplc retention times of the desired products from anthranilic acid 2. For example, Table 3 indicates that anthranilic acid 2 reacted with amine 3 and aldehyde 15 affords the desired product with a retention time of 4.01, under the conditions mentioned above.

TABLE 3

	3	4	5	6	7	8	9	10	11	12	13	14
15	4.01	4.09	4.45	4.01	3.79	4.36	2.95	3.30	4.84	-	4.62	2.95
16	4.97	5.15	5.46	4.89	4.93	5.28	3.87	4.36	5.68	3.92	5.46	4.27
17	4.49	4.67	4.93	4.49	4.45	4.84	3.52	3.96	5.24	3.57	5.02	3.83
18	3.83	4.05	4.36	3.83	3.61	4.27	2.73	3.26	4.75	2.91	4.49	3.04

94

19	4.23	4.36	4.67	4.23	4.05	4.58	3.17	3.56	5.06	-	4.80	3.48
20	4.36	4.62	4.84	4.36	4.40	4.71	3.43	3.92	5.06	-	4.97	3.70
21	5.28	5.46	5.81	5.20	5.28	5.59	4.18	4.67	6.03	3.83	5.50	4.62
22	3.61	3.96	4.23	3.79	3.57	4.14	2.77	3.26	4.39	2.51	4.40	3.04

Table 4 contains molecular weight of the desired products from anthranilic acid 2. Desired products are seen as (M+ 1). For example, Table 4 indicates that anthranilic acid 2 reacted with amine 3 and aldehyde 15 affords the desired product with a molecule weight (M+1) of 322.4, under the conditions mentioned above.

TABLE 4

	3	4	5	6	7	8	9	10	11	12	13	14
15	322.4	336.4	316.4	352.4	288.4	350.5	340.4	415.5	378.5	359.4	412.5	357.5
16	364.5	378.5	358.5	394.5	330.5	392.5	382.5	457.6	420.6	401.5	454.6	399.5
17	384.5	398.5	378.5	414.5	350.5	412.5	402.5	477.6	440.6	421.5	474.6	419.5
18	308.4	322.4	302.4	338.4	274.4	336.4	326.4	401.5	364.5	345.4	398.5	343.4
19	336.4	350.5	330.5	366.5	302.4	364.5	354.5	429.5	392.5	373.5	426.5	371.5
20	442.5	456.5	436.5	472.5	408.5	470.6	460.5	535.6	498.6	479.5	532.6	477.6
21	404.6	418.6	398.6	434.6	370.5	432.6	422.6	497.7	460.7	441.6	494.7	439.6
22	392.5	406.5	386.5	422.5	358.4	420.5	410.5	485.6	448.6	429.5	482.6	427.5

Table 5, Note: For A% yields x/y : The first yield "x" represents that for reactions with *N*-BOC anthranilic acid, 1. The second yield "y" represents that for *N*-Me-BOC anthranilic acid, 2. Row 15 represents yields of reactions with aldehyde 15. Column 3 represents yields of reactions with amine 3. For example, Table 5 indicates that anthranilic acid 1 reacted with amine 3 and aldehyde 15 affords the desired product with a yield 40%, under the conditions mentioned above.

TABLE 5

	3	4	5	6	7	8	9	10	11	12	13	14
15	40/16	40/29	40/27	54/15	40/25	39/40	26/16	18/21	41/15	1/0	39/31	47/30
16	85/87	82/72	77/64	79/72	82/69	84/67	81/73	78/67	82/74	43/10	88/74	84/73
17	88/84	85/73	89/68	92/81	92/78	88/68	90/75	82/73	84/79	39/8	76/77	85/72
18	87/80	72/52	69/43	79/70	70/41	80/51	87/63	81/64	81/70	51/25	75/60	80/62
19	45/10	37/24	39/22	36/12	34/20	33/12	41/7	28/26	44/10	9/0	37/16	39/20
20	79/49	74/61	63/51	75/12	66/53	69/54	59/10	74/61	83/67	6/0	71/49	67/64
21	89/87	86/69	88/66	85/82	89/63	85/70	90/74	83/69	86/84	38/8	84/74	88/78
22	85/64	86/63	80/67	85/82	84/75	85/64	82/69	84/67	86/75	27/11	84/69	83/61

95

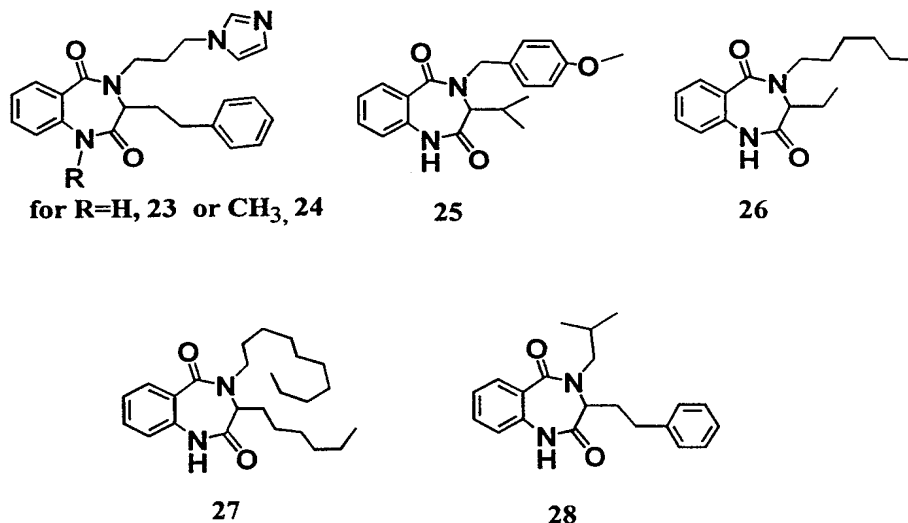
EXAMPLE 2General Solid Phase Synthesis of Compounds of Formula (I) using the Ugi reaction and resin (IXa)

5 (60mg) of resin (IXa) is pre-swelled with THF. 0.5M solutions of the aldehyde (XV) (10 equiv.), amine (XVI) (10 equiv.) and carboxylic acid (XIV) (10 equiv.) in THF:MeOH (1:1) are added sequentially to the resin (IXa) and the reaction stirred at room temperature for 3 days. The resin is washed sequentially with CH₂Cl₂, THF, DMF, THF and MeOH dried under high vacuum to yield the resin bound Ugi product (IXa) Treatment with BOC₂O (10 equiv.), Et₃N (10 equiv.) and DMAP in

10 CH₂Cl₂ (15 hours) afforded the activated resin (XX) for cleavage. Sodium methoxide (5mg) in THF: MeOH, 1:1, is added to the resin and shaken for 20 hours. The solvent is evaporated in vacuo to give the desired methyl ester (XXI). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane. The samples are then evaporated in a SAVANT at room temperature for 3 hours to give the crude product of formula

15 (I). Examples of products (examples 23 to 28) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a Hypersil BDS 3 m C18 4.6X50mm 0.1%TFA in H₂O/CH₃N 10% to 100% CH₃N 5 min, at a rate of 1ml/min for 23-28. Desired products are seen as (M+ 1).

20



Compound	Retention time	mass spec	ELSD A%	UV (220 nm) A%
23	3.36	388	>90	>90
24	3.62	402	90	>90
25	3.93	338	90	80

96

26	4.27	288	90	91
27	6.48	400	95	91
28	4.36	336	89	80

EXAMPLE 3

Solution Phase Synthesis of Compounds of Formula (II) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components compound of formulae (XXII), (XV), (XVI) and (IXb), are employed generating a theoretical 10 μ mol of final diketopiperazine product (II) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and a 5% solution of diethylamine in dichloroethane [Note : 10-15 mg of N,N-(diisopropyl)amino-methylpolystyrene (PS-DIEA) is an excellent resin bound alternative to diethylamine]. Solvents are then evaporated at 65 °C to afford the cyclized products of formula(II).

EXAMPLE 4

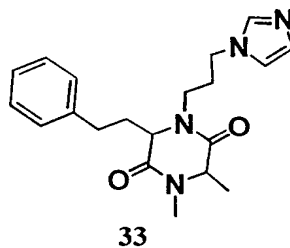
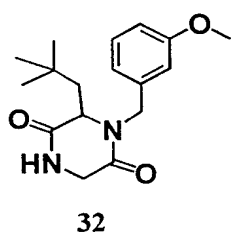
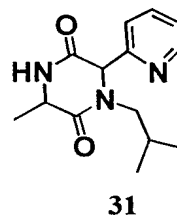
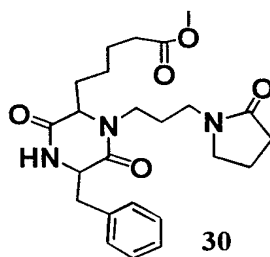
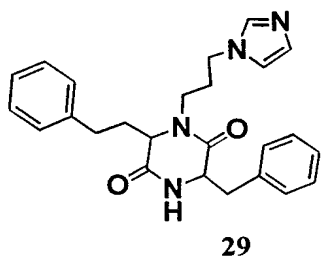
General Solid Phase Synthesis of Compounds of Formula (II) using the Ugi reaction and resin (IXa)

(60mg) of resin (IXa) is pre-swelled with THF. 0.5M solutions of the aldehyde (XV) (10 equiv.), amine (XVI) (10 equiv.) and carboxylic acid (XXII) (10 equiv.) in THF:MeOH (1:1) are added sequentially to the resin (IXa) and the reaction stirred at room temperature for 3 days. The resin is washed sequentially with CH₂Cl₂, THF, DMF, THF and MeOH dried under high vacuum to yield the resin bound Ugi product (XXIII). Treatment with BOC₂O (10 equiv.), Et₃N (10 equiv.) and DMAP in CH₂Cl₂ (15 hours) affords the activated resin bound product (XXIV) for cleavage. Sodium methoxide (5mg) in THF: MeOH, 1:1, is added to the resin and shaken for 20 hours. The solvent is evaporated in vacuo to give the desired methyl ester (XXV). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and a 5% solution of diethylamine in dichloroethane [Note : 10-15 mg of N,N-(diisopropyl)amino-methylpolystyrene (PS-DIEA) is an excellent resin bound alternative to diethylamine]. Solvents are then evaporated at 65 °C to afford the cyclized product of formula (II). Examples of products (examples 29 to 33) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18

97

Hypersil BDS 3 m C18 4.6X50mm 0.1%TFA in H₂O/CH₃N 10% to 100% CH₃N 5 min, at a rate of 1ml/min for 29-33. Desired products are seen as (M+ 1).

98



Compound	Retention time	Mass spec	ELSD A%	UV (220 nm) A%
29	3.19 & 3.36	416	100	71
30	3.10	443	94	68
31	2.80	261	100	95
32	3.10 & 3.76	304	98	89
33	3.02 & 3.10	354	71	56

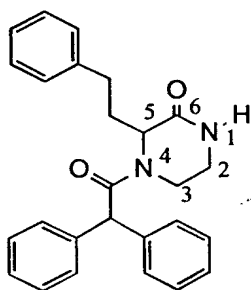
5 EXAMPLE 5

Solution Phase Synthesis of Compounds of Formula (III) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

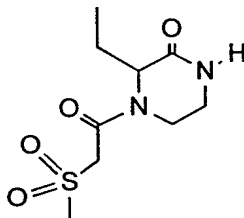
- 10 Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components compound of formulae (XXVI), (XXVII), (XV) and (IXb), are employed generating a theoretical 10 μ mol of final product for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol,
- 15 or a 10% solution of trifluoroacetic acid in dichloroethane, and a 5% solution of diethylamine in dichloroethane [Note : 10-15 mg of N,N-(diisopropyl)amino-methylpolystyrene (PS-DIEA) is an excellent resin bound alternative to diethylamine]. Solvents are then evaporated at 65 °C to afford the cyclized product of formula (III). Examples of products (examples 34 to 45) synthesized using this

99

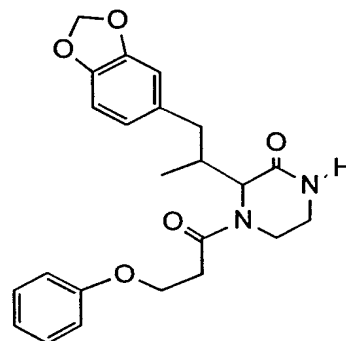
general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 2.1 x 50 mm column (UV 220 nm) with a mobile phase of 0.1% TFA in CH₃CN/H₂O, gradient from 10% CH₃CN to 100% over 5 min. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products seen as (M+1).



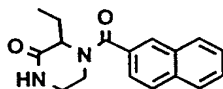
34



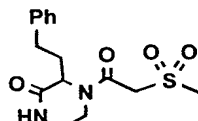
35



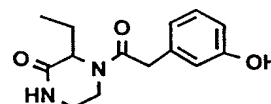
36



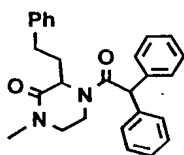
37



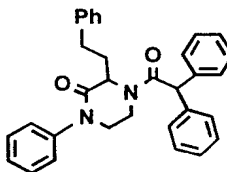
38



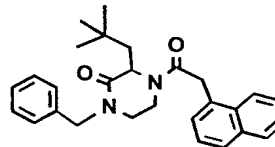
39



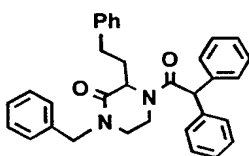
40



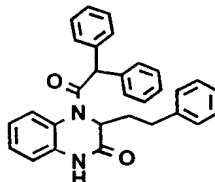
41



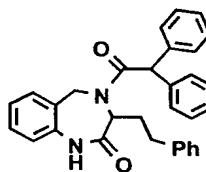
42



43



44



45

10

Compound	Retention time	Mass spec	UV (220 nm) A%
34	6.66	398	77
35	1.06	248	97

100

36	4.09	394	92
37	3.35	282	77
38	2.91	324	77
39	2.38	262	69
40	4.14	412	83
41	5.07	474	70
42	4.60	428	80
43	5.26	488	85
44	5.19	446	66
45	5.14	460	30

General Procedure and ^1H for compound 34

Stoichiometric amounts (2 ml) of 0.1 M solutions of the four Ugi components are combined and stirred at room temperature overnight. The solvent is evaporated *in vacuo* and the residue is dried under high vacuum. A 10% solution of AcCl in MeOH (8 ml) is added to the crude material and stirred at room temperature overnight. The solvent is evaporated in *vacuo*. A 5% solution of diethylamine in dichloroethane is then added to the crude material and the solution shaken overnight at room temperature. The solvent is evaporated in *vacuo* and crude material pre-absorbed onto flash silica and purified by column chromatography to yield the desired ketopiperazine, **34**, (44 mg, 55%) as a white solid : mp 188-190°C. For major conformer only: ^1H (CDCl_3) 7.90 (1H, s, NH), 7.10-7.40 (15H, m, $\text{C}_6\text{H}_5 \times 3$), 5.60 (1H, s, CHC_6H_5), 4.78-4.83 (1H, m, CHCH_2), 4.05-4.12, 3.31-3.40 (2H, 2x m, CH_2N), 2.98-3.02, 2.80-2.88 (2H, 2x m, CH_2N), 2.50-2.60 (2H, m, $\text{CH}_2\text{C}_6\text{H}_5$), 1.90-2.00, 2.03-2.10 (2H, CH_2). For major conformer only: ^{13}C (CDCl_3) 170.2, 168.7, 141.4, 139.8, 128.7, 128.4, 128.3, 126.7, 125.8, 54.5, 53.0, 39.2, 32.9, 31.7. IR (KBr disc) 3260m, 1641s, 1620s (selected peaks only). mspec (APCI) 399 (MH^+), 371. ^1H and ^{13}C assignments have been obtained from ^1H , ^{13}C , DEPT, COSY, HMQC and HMBC experiments. The ^1H and ^{13}C spectra show two sets of resonances throughout the spectrum. Exchange crosspeaks between major and minor forms are observed in a rotating frame Overhauser effect spectroscopy (ROESY). These resonances also show broadening at temperatures above 80°C. These experiments show that the two forms are in slow exchange under the present experimental conditions. HMBC spectrum showed correlation between the methylene protons(H_2 and H_2') with the carbonyl carbon C6 confirming the ring closure.

EXAMPLE 6

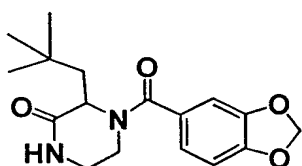
General Solid Phase Synthesis of Compounds of Formula (III) using the Ugi reaction and resin (IXa)

(60mg) of resin (IXa) is pre-swelled with THF. 0.5M solutions of the aldehyde (XV) (10 equiv.), diamine (XXVII) (10 equiv.) and carboxylic acid (XXVI) (10 equiv.) in THF:MeOH (1:1) are added sequentially to the resin (IXa) and the reaction stirred at room temperature for 3 days. The resin is

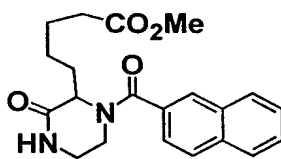
101

washed sequentially with CH_2Cl_2 , THF, DMF, THF and MeOH dried under high vacuum to yield the resin bound Ugi product (XXX). Treatment with BOC_2O (10 equiv.), Et_3N (10 equiv.) and DMAP in CH_2Cl_2 (15 hours) afford the activated the resin bound product (XXVII) for cleavage. Sodium methoxide (5mg) in THF: MeOH, 1:1, is added to the resin and shaken for 20 hours. The solvent is evaporated in vacuo to give the desired methyl ester (XXXI). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane. Solvents are then evaporated at 65°C to afford the cyclized product of formula (III). Examples of products (examples 46 to 51) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD

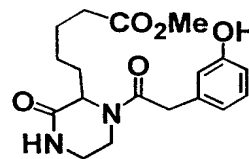
(evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a Hypersil BDS 3 m C18 4.6X50mm 0.1%TFA in $\text{H}_2\text{O}/\text{CH}_3\text{N}$ 10% to 100% CH_3N 5 min, at a rate of 1ml/min for 46-49 and 51. C18 Hypersil BDS 3 m C18 4.6X50mm 0.1%TFA in $\text{H}_2\text{O}/\text{CH}_3\text{N}$ 5% to 100% CH_3N 5 min, at a rate of 1ml/min for 52. Desired products are seen as (M+ 1).



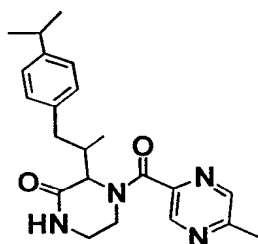
46



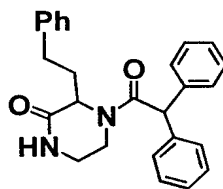
47



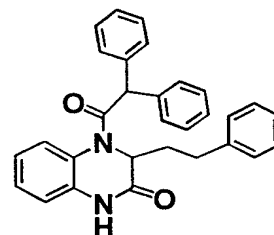
48



49



50



51

15

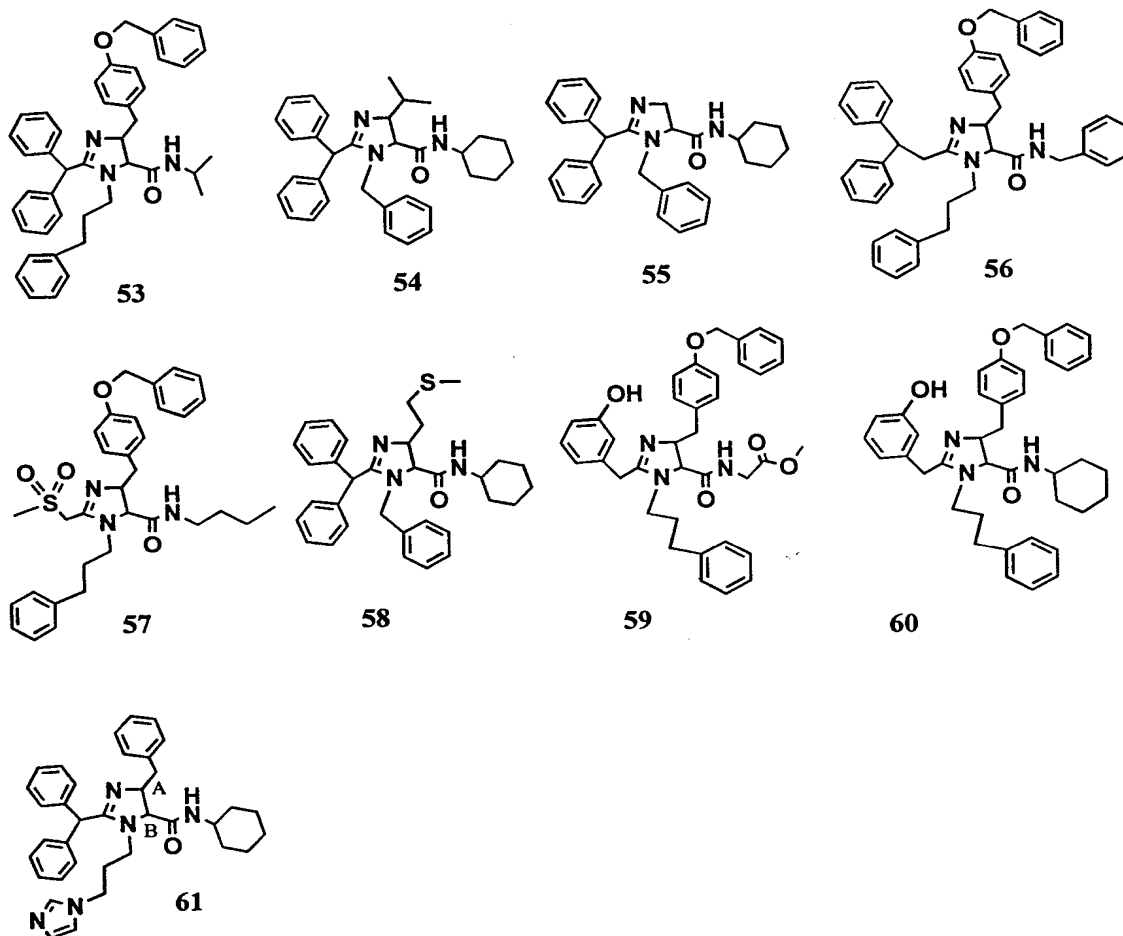
Compound	Retention time	Mass spec	ELSD A%	UV (220 nm) A%
46	3.54	318	100%	100%
47	3.63	368	100%	100%
48	2.80	348	100%	94%
49	4.19	380	100%	100%
50	7.55	398	100%	77%
51	5.19	446	80%	86%

EXAMPLE 7

General Solution Phase Synthesis of Compounds of Formula (IV) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

- 5 Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components compounds of formulae (IX), (XV), (XVI) and (XXXIII) are employed generating a theoretical 10 μ mol of dihydroimidazole product (IV) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane. Solvents are then evaporated at 65 °C to afford the cyclized product of formula (IV). The non-cyclized amines were removed via a solution phase scavenging step with the simultaneous addition of PS-DIEA or PS-tris(2-aminoethyl)amine (6 equiv.) and PS-NCO (3 equiv.) in dichloroethane. (Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* 1997, 119, 4882. Flynn, D.L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodward, S. *J. Am. Chem. Soc.* 1997, 119, 4874. Purchased from Argonaut® technologies (PS-DIEA - polystyrene bound diisopropylethylamine)). Examples of products (examples 53 to 61) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 15 min, at a rate of 1ml/min for 3, 6, 7, 9, 10 and 11. BDS Hyp. 3 m C18 4.6X50mm 0.1% TFA IN H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min for 4, 5, 8. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).
- 10
- 15
- 20

103



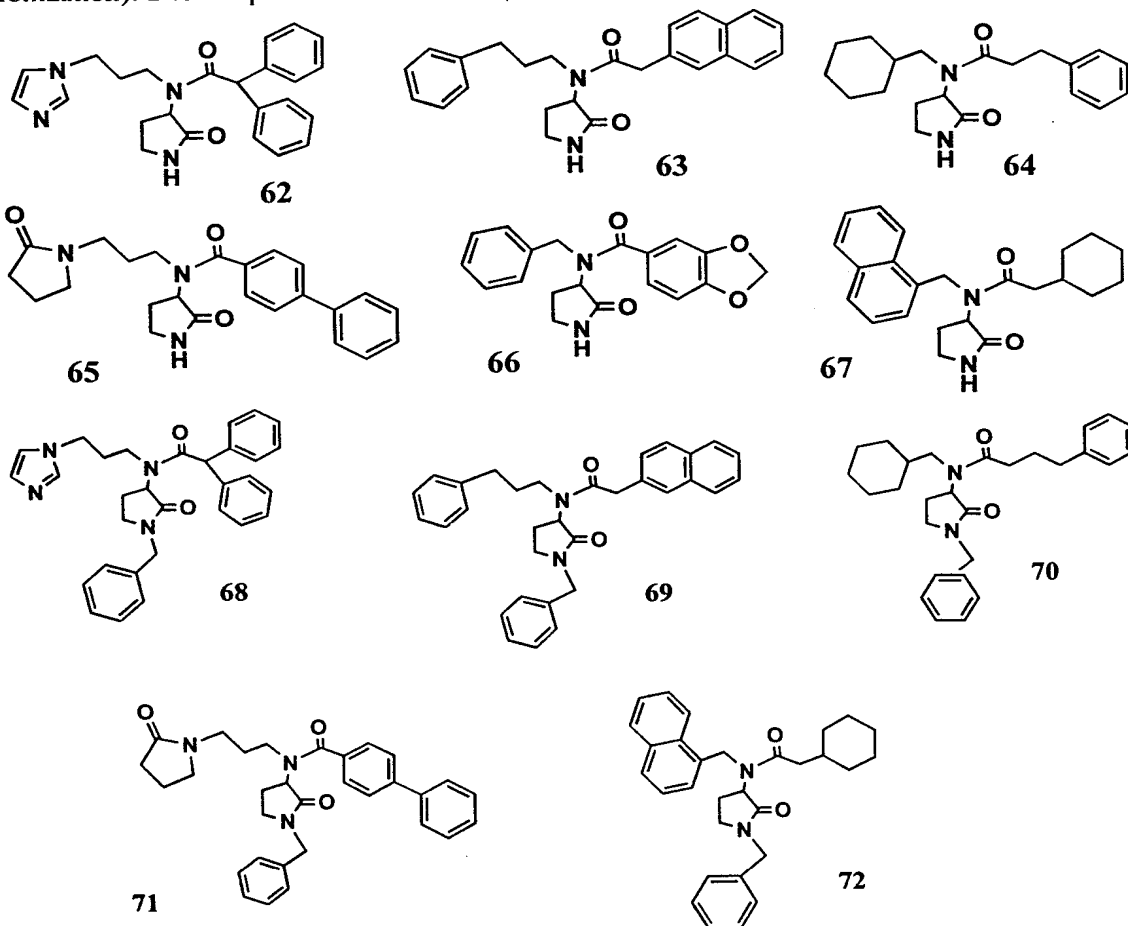
Compound	Retention time	mass spec	UV (220 nm) A%
53	7.36 & 8.05	625	40
54	4.87 & 5.08	493	66
55	4.58	451	60
56	11.26 & 1.57	697	67
57	6.36 & 6.84	565	59
58	4.86 & 5.03	525	79
59	8.53	605	56
60	10.0 & 10.22	615	48
61	8.05 & 8.88	665	71

EXAMPLE 8

5 General Solid Phase Synthesis of Compounds of Formula (V) using the Ugi reaction and resin (XVIII)

104

(60mg) of resin (XVIII) is pre-swelled with THF. 0.5M solutions of the aldehyde (XV) (10 equiv.), N-BOC-amino aldehyde (XXXV) (10 equiv.) and amine (XVI) (10 equiv.) in THF:MeOH (1:1) are added sequentially to the resin (XVIII) and the reaction stirred in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The resin is washed sequentially with CH₂Cl₂, THF, DMF, THF and MeOH dried under high vacuum to yield the resin bound Ugi product (XXXVI). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane. Cyclization is then effected by base treatment with a 5% solution of diethylamine in dichloroethane [Note : 10-15 mg of N,N-(diisopropyl)amino-methylpolystyrene (PS-DIEA) is an excellent resin bound alternative to diethylamine]. Solvents are then evaporated at 65 °C to afford the cyclized products. Examples of products synthesized using this general methodology are indicated below. Lc/ms (liquid chromatography/mass spectrometry) analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 15 min, at a rate of 1ml/min for 62. Hypersil BDS 3 m C18 4.6X50mm 0.1% TFA IN H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min for 63 to 72. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).



105

Compound	Retention time	mass spec	Compound	Retention time	mass spec
62	4.88	402	68	10.75	492
63	4.34	386	69	15.79	476
64	4.30	328	70	16.59	432
65	3.33	405	71	11.22	495
66	3.47	338	72	16.86	454
67	4.56	364			

Example 9

General Solution Phase Synthesis of 1,4-benzodiazepine-2,5-dione Compounds of Formula (VI) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

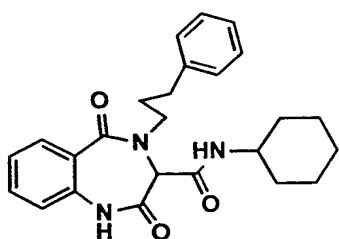
5

Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components, ethyl glyoxalate (XXXVII), compound of formulae (XIV), (XVI) and (IX), are employed generating a theoretical 10 μ mol of final 1,4-benzodiazepine-2,5-dione product (VI) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours) . The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and heat, to afford the cyclized products. Examples of products (examples 62 to 72) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% . Lc/ms (liquid chromatography/mass spectrometry) analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).

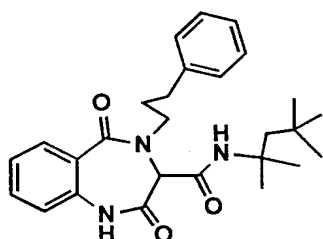
10

15

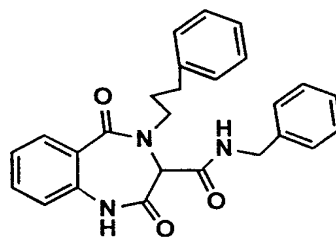
106



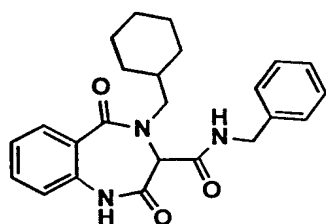
73



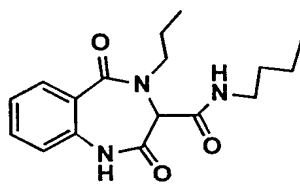
74



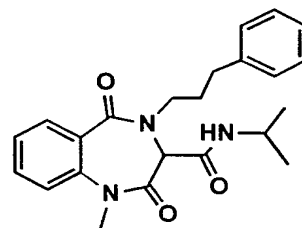
75



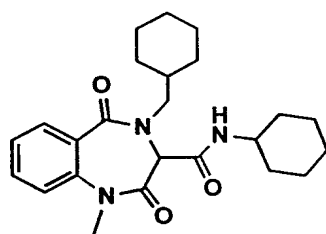
76



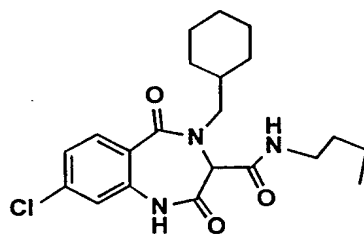
77



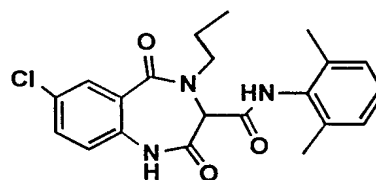
78



79



80



81

Compound	Retention time	mass spec	ELSD A%
73	4.26	419	82
74	4.93	449	83
75	4.10	427	90
76	4.06	405	89
77	3.16	317	39
78	4.00	393	27
79	4.47	411	63
80	4.30	455	60
81	3.97	399	84

Example 10

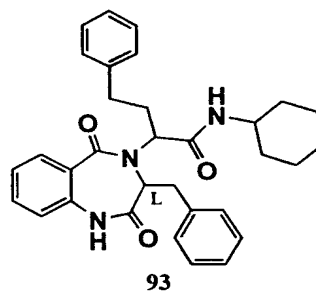
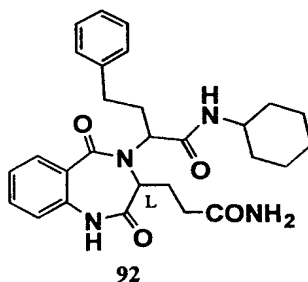
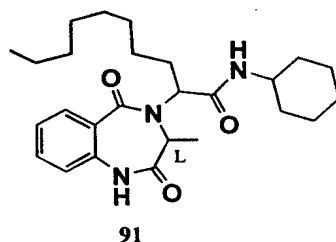
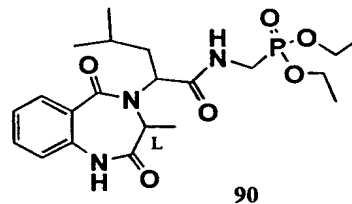
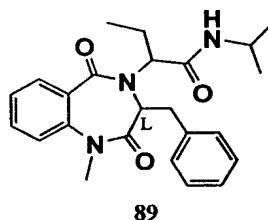
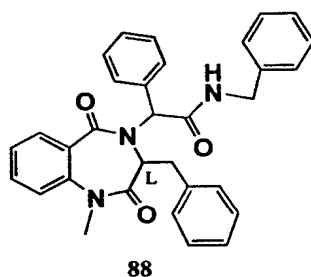
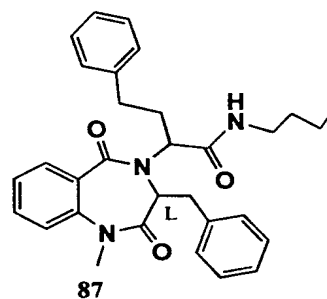
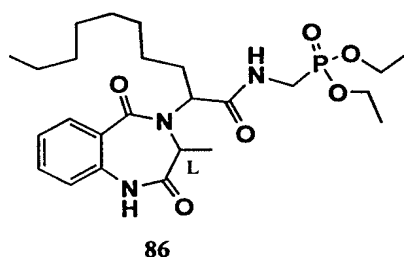
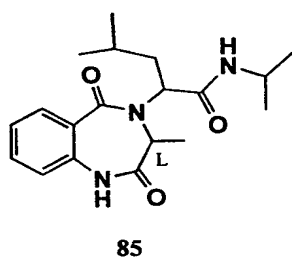
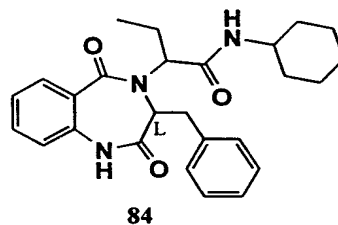
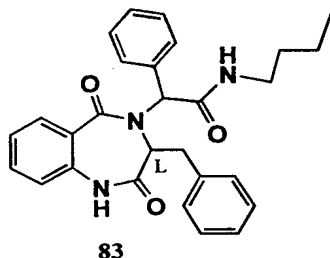
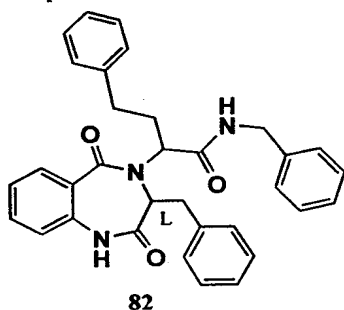
5 General Solid Phase Synthesis of Compounds of Formula (VII) using the Ugi reaction and Resin Bound Amine (XXXIX)

Wang bound Fmoc-amino acids (XXXIX) (100mg : loading of 0.70mmol/g) are treated with 20% piperidine in DMF (1 ml) at room temperature for one hour and washed with DMF (x3) and CH₂Cl₂ (x3). To each reaction vessel containing (XXXIX) is added 0.8 ml of CH₂Cl₂, followed by 0.1M solutions in MeOH of aldehydes (XV) (5 equiv.), isonitriles (IX) (5 equiv.) and anthranilic acid (XIV) (5 equiv.). The reactions are shaken overnight at room temperature and washed with methanol (x3) and CH₂Cl₂ (x3). Each resin is then treated with 10% TFA in CH₂Cl₂ at room temperature for 3 hours (1.3 ml), then washed with CH₂Cl₂ (x2). The samples are then evaporated in a SAVANT at room temperature for 3 hours to give the crude products. Examples of products (examples 82 to 93) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A%. Lc/ms (liquid chromatography/mass spectrometry) analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 20% to 100% 20 min, at a rate of 1ml/min. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).

The following specific procedure is followed for compound 82 :-

Wang bound Fmoc-Phenylalanine (100mg : loading of 0.70mmol/g) is treated with 20% piperidine in DMF (1 ml) at room temperature for one hour and washed with DMF (x3) and CH₂Cl₂ (x3). To each reaction vessel is added 0.8 ml of CH₂Cl₂, followed by 0.1M solutions in MeOH of

phenpropionaldehyde (46 μ l, 5 equiv.), benzyl isocyanide (43 μ l, 5 equiv.) and N-BOC anthranilic acid (83mg, 5 equiv.). The reactions are shaken overnight at room temperature and washed with methanol (x3) and CH₂Cl₂ (x3). Each resin is then treated with 10% TFA in CH₂Cl₂ at room temperature for 3 hours (1.3 ml), then washed with CH₂Cl₂ (x2). The sample is then evaporated in a SAVANT at room temperature for 3 hours to give 20mg of crude product.



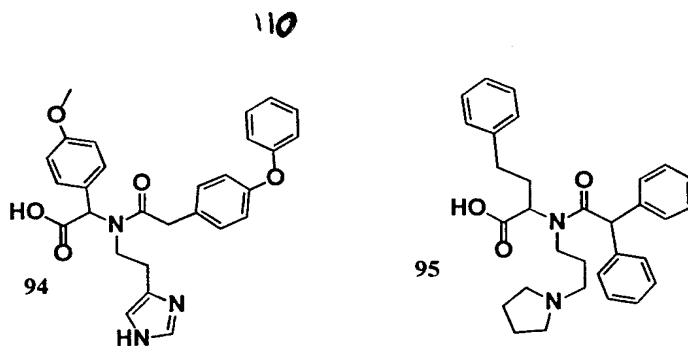
109

Compound	Retention time	Mass spec	ELSD A%
82	10.45	517	70
83	8.68 & 9.18	455	95
84	8.24 & 9.08	433	97
85	4.90 & 5.40	345	95
86	8.31 & 9.51	509	50
87	10.88 & 11.25	497	100
88	9.58 & 10.08	503	95
89	7.14 & 7.37	407	41
90	4.07 & 5.14	453	44
91	11.88 & 12.28	441	44
92	6.54 & 6.77	490	100
93	9.38 & 10.35	481	100

Example 11

5 General Solid Phase Synthesis of Acids by Hydroxide Clipping of Resin Bound Safety Catch Linker (IXa)

(60mg) of resin (IXa) is pre-swelled with THF. 0.5M solutions of the aldehyde (XV) (10 equiv.), amine (2-(5-imidazole)ethylamine or 3-(1-pyrrolidine)propylamine) (10 equiv.) and carboxylic acid (XXVI) (10 equiv.) in THF:MeOH (1:1) are added sequentially to the resin (IXa) and the reaction stirred at room temperature for 3 days. The resin is washed sequentially with CH₂Cl₂, THF, DMF, THF and MeOH dried under high vacuum to yield the resin bound Ugi products. Treatment with BOC₂O (10 equiv.), Et₃N (10 equiv.) and DMAP in CH₂Cl₂ (15 hours) afford the activated the resin bound product. Sodium hydroxide (5mg) in THF:H₂O, 1:1, is added to the resin and shaken for 20 hours. The solvent is evaporated in vacuo to afford the desired acid, where lc/ms (liquid chromatography/mass spectrometry) A% purities are judged by ELSD (evaporative light scattering detector) A%. Lc/ms analysis is performed using a Hypersil BDS 3μ C18 4.6X50mm 0.1%TFA in H₂O/CH₃N 5% to 100% CH₃N 5 min, at a rate of 1ml/min. Desired products are seen as (M+ 1). Examples of acids synthesized using this general methodology are:



Compound	Retention time	mass spec	ELSD A%
94	4.80	485	100
95	4.23	484	89

5 Example 12

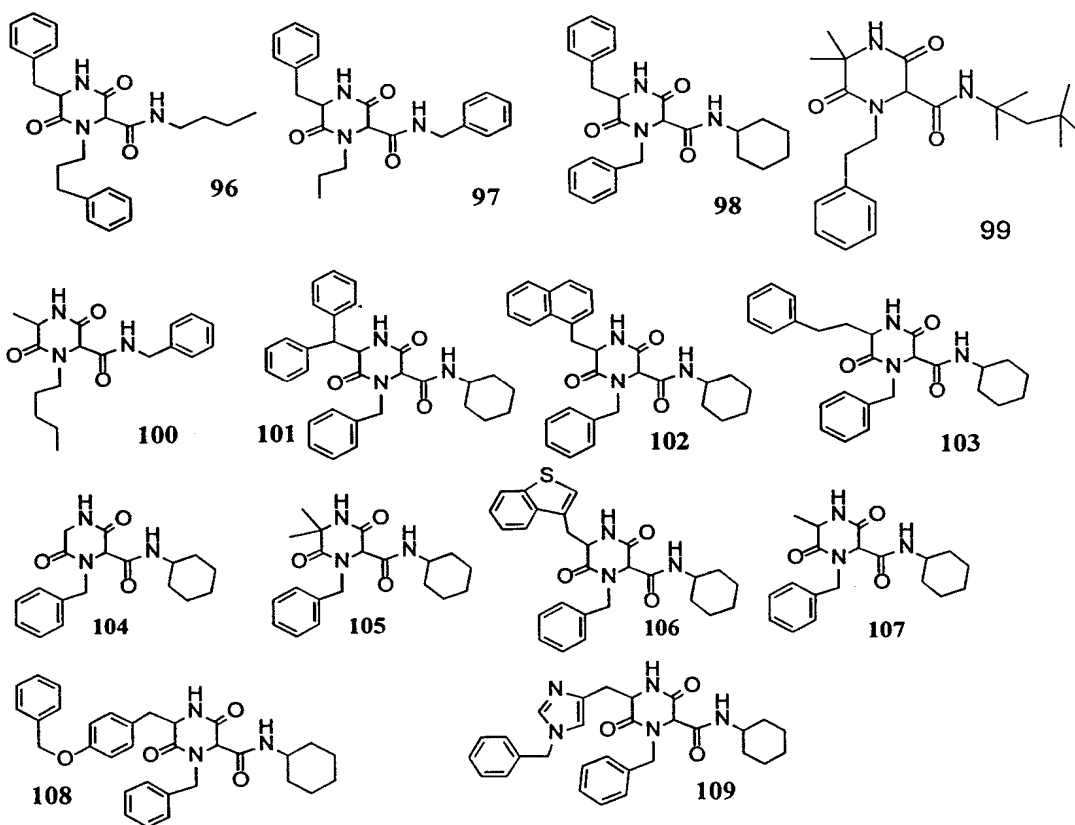
General Solution Phase Synthesis of Diketopiperazine Compounds of Formula (VI) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

- Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components compound of formulae (XIV), (XXXVII), (XVI) and (IX), are employed generating a theoretical 10 μ mol of final Diketopiperazine product (VI) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and heat, to afford the cyclized products. Examples of products (examples 96 to 112) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min (Examples 96 to 99), or a mobile phase 5mM NH₄OAC.H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min (Examples 100 to 112),. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).

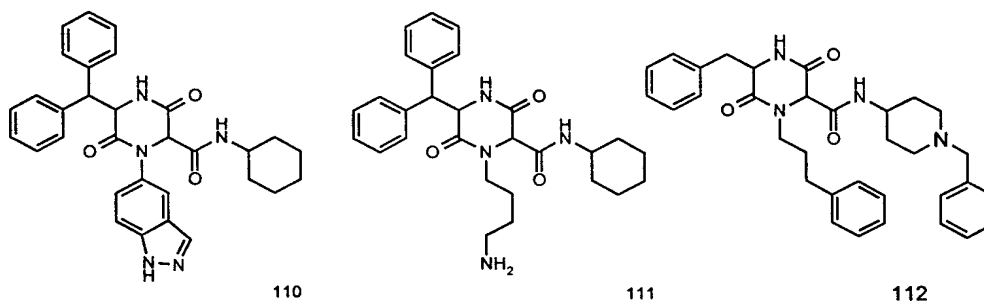
Compound	UV (220 nm) A%	ELSD A%	Retention Time (min)	Mass spec
96	80	70	4.33	421
97	75	90	3.80	379
98	81	90	4.27/4.40	419

111

99	80	90	3.83	379
100	86	100	3.13	303
101	86	100	4.90	495
102	84	100	4.57/4.80	469
103	92	100	433	4.60
104	72	100	329	3.53
105	83	100	357	3.80
106	81	100	475	4.53/4.77
107	82	100	343	3.67
108	88	100	449	4.39/4.49
109	95	70	499	3.89/3.96
110	80	90	3.88/4.22	521
111	70	86	3.78/3.51	476
112	63	84	3.50/3/63	538



112

**Example 13**

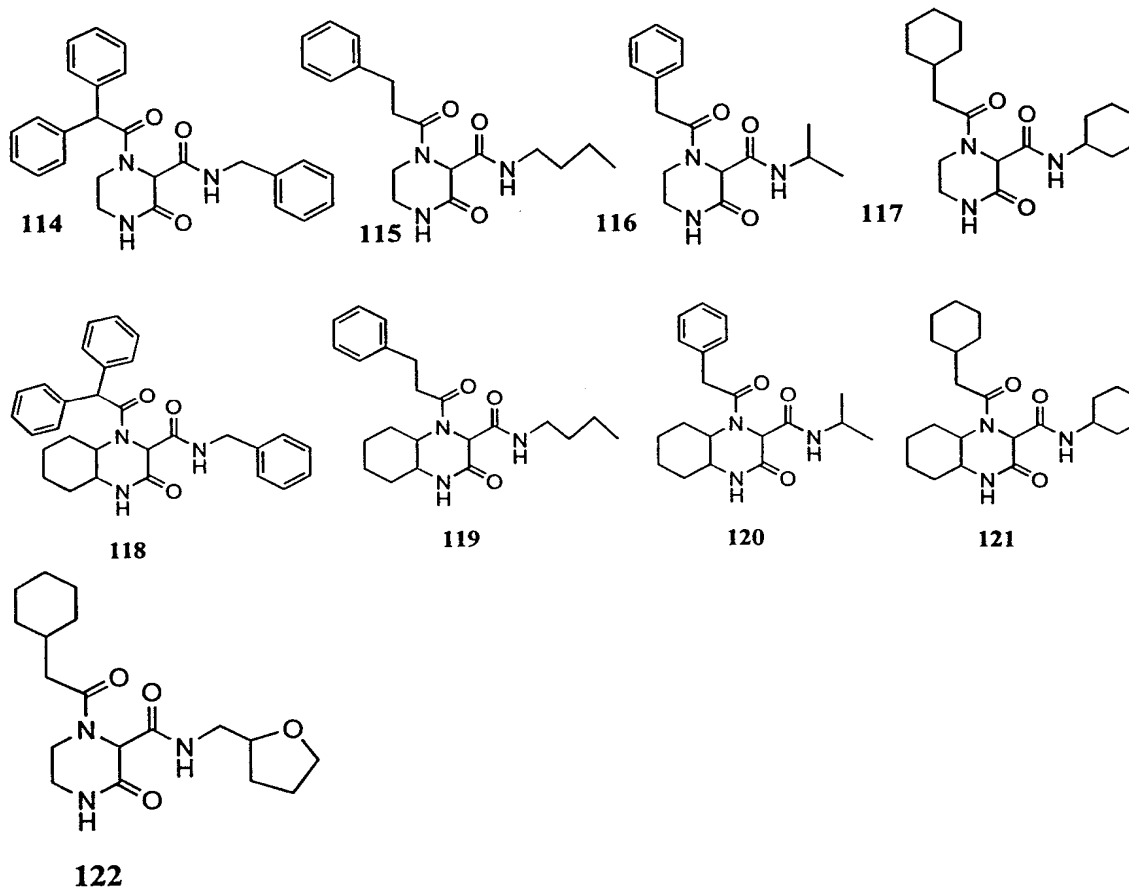
General Solution Phase Synthesis of Ketopiperazine Derivatives of Formula (VIII) via the '2-step, one pot' procedure, employing the Ugi multi-component reaction:

Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components compound of formulae (XXVI), (XXXVII), (XXVIIa) and (IX) are employed generating a theoretical 10 μ mol of final product (VIII) for 100% conversion. The 4-component condensation is performed in methanol at room temperature followed by increased heating, to afford the cyclized products. Examples of products (examples 113 to 122) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase 0.1% TFA IN H₂O/CH₃CN 10% to 100% 5 min, at a rate of 1ml/min. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).

Compound	UV (220 nm) A%	ELSD A%	Mass spec	Retention Time (min)
114	41%	90%	427	4.17
115	43%	97%	331	3.53
116	35%	96%	303	2.90
117	32%	94%	349	3.97
118 cis	41%	90%	481	4.60
118 trans	70%	99%	481	4.63
119 cis	43%	97%	385	3.36/3.83
119 trans	47%	100%	385	4.09
120 cis	35%	96%	357	3.36/3.46
120 trans	34%	100%	357	3.63
121 cis	32%	94%	403	4.37/4.54
121 trans	57%	100%	403	4.67

115

122	75%	100%	351	3.29
-----	-----	------	-----	------



5

Example 14

General Solution Phase Synthesis of Ketopiperazine Derivatives of Formula (VIII) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

10

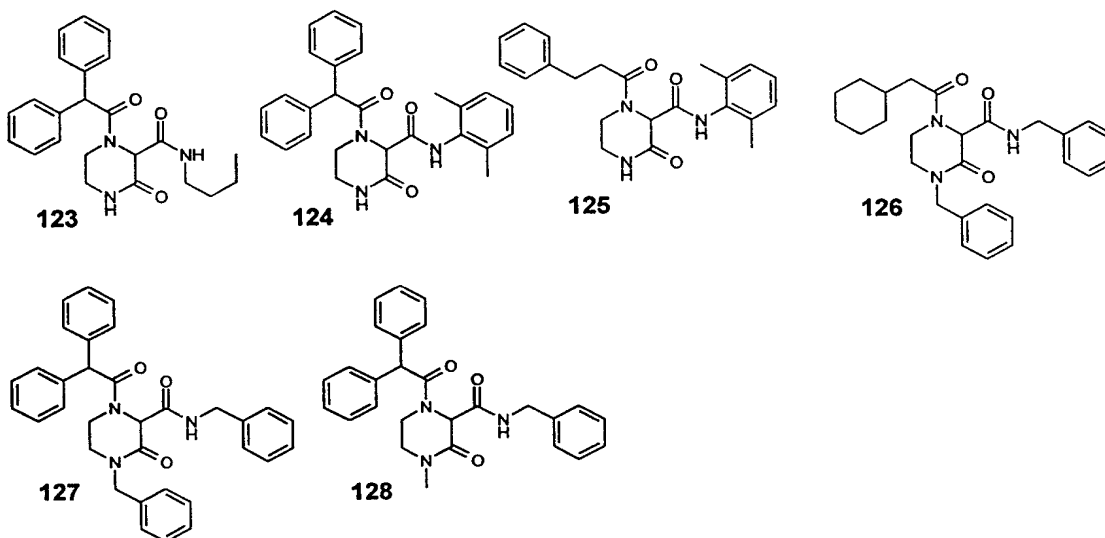
Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components, compound of formulae (XXVI), (XXXVII), (XXVII) and (IX), are employed generating a theoretical 10 μ mol of final Ketopiperazine product (VIII) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using the intermediate (XLI) and either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and heat, to afford the acyclic products. MP-carbonate (3 equiv.) in dichloroethane (0.4ml) is added to the crude product and stirred overnight. The resin is filtered and washed with dichloroethane and then the filtrate is evaporated at 65°C for 2 hours. Examples of products (examples 123 to 129) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid

20

114

chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%..
 Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a
 mobile phase :- 0.1% AQ/ACN 10% to 100%, 5 min. (Compounds 123 and 124); 0.1% AQ/ACN 0% to
 100%, 10min (compounds 125-128). HPLC is interfaced with APCI techniques (Atmospheric Pressure
 5 Chemical Ionization). Desired products are seen as (M+ 1).

Compound	UV (220 nm) A %	ELSD A %	Mass spec	Retention Time (min)
123	85	100	379	4.05
124	46	78	441	4.30
125	50	77	379	3.82
126	52	31	447	4.84
127	94	100	517	4.93
128	62	79	441	4.37



10

Example 15

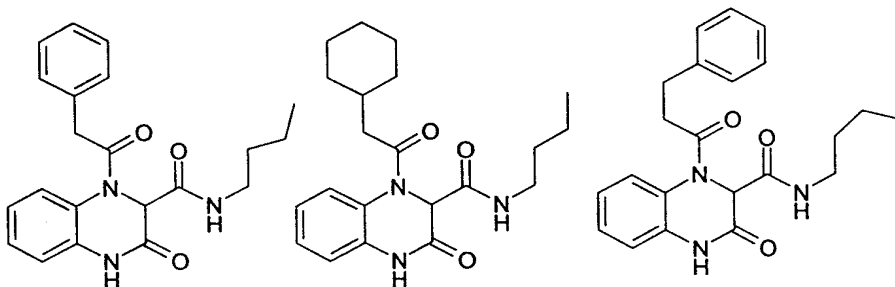
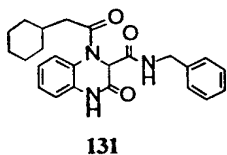
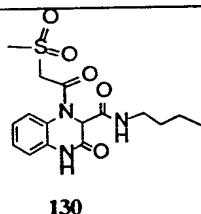
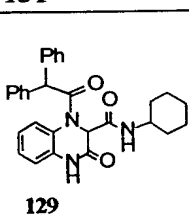
General Solution Phase Synthesis of Dihydroquinoxalinone Derivatives of Formula (VIII) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

15

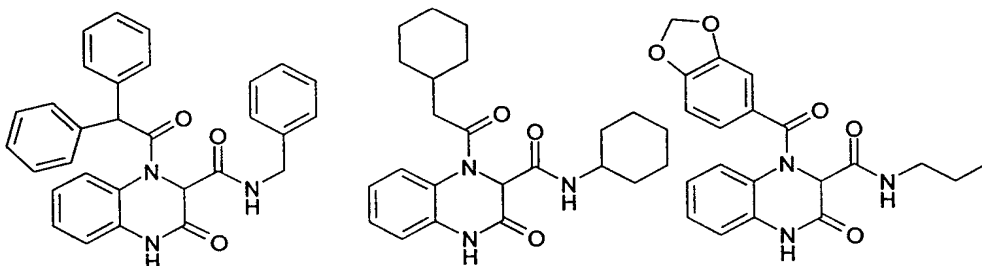
Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components, compound of formulae (XXVI), (XXXVII), (XXVII) and (IX), are employed generating a theoretical 10 μ mol of final Dihydroquinoxalinone product (VIII) for 100% conversion. The 4-component condensation is

performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT[®] evaporator for 2 hours). The deprotection/cyclization steps are performed using either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and heat, to afford the cyclized products. Examples of products synthesized and further examples of other products which could be formed using this general methodology are indicated below. Examples of products (examples 129 to 131) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile 0.1% AQ/ACN 0% to 100%, 5 min. HPLC is interfaced with APCI techniques (Atmospheric Pressure Chemical Ionization). Desired products are seen as (M+ 1).

Compound	UV (220 nm) A%	ELSD A%	Mass spec	Retention Time (min)
129	30	28	467	5.17
130	40	43	367	3.03
131	30	20	405	4.04



116

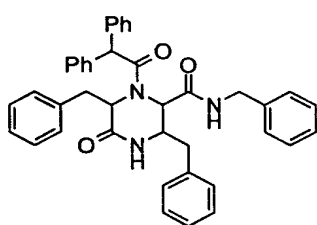
**Example 16**

General Solid Phase Synthesis of Ketopiperazine Derivatives of Formula (XLII) via the '3-step, one pot' procedure, employing the Ugi multi-component reaction:

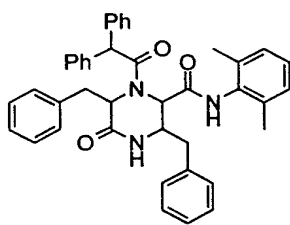
- 5 Wang bound Fmoc-amino acids (XXXIX) (100mg : loading of 0.70mmol/g) is treated with 20% piperidine in DMF (1 ml) at room temperature for one hour and washed with DMF (x3) and CH₂Cl₂ (x3). Equal amounts (0.1ml) of 0.1 M solutions of the four appropriate components, compound of formulae (XXVI), (XXXIX), (XLIII) and (IX), are employed generating a theoretical 10 μmol of final
- 10 Ketopiperazine product (XLII) for 100% conversion. The 4-component condensation is performed in methanol at room temperature and the solvent evaporated at 65 °C (using a SAVANT® evaporator for 2 hours). The deprotection/cyclization steps are performed using the intermediate (XLIX) and either a 10% solution of acetyl chloride in methanol, or a 10% solution of trifluoroacetic acid in dichloroethane, and heat, to afford the cyclized products. Examples of products synthesized using this general methodology
- 15 are indicated below. Examples of products (examples 132 to 139) synthesized using this general methodology are indicated below and purities are determined by lc/ms (liquid chromatography/mass spectrometry) ELSD (evaporative light scattering detector) A% and UV A%. Lc/ms analysis is performed using a C18 Hypersil BDS 3 m 4.6X50mm column (UV 220 nm) with a mobile phase :- 0.1% AQ/ACN 10% to 100%, 5 min. HPLC is interfaced with APCI techniques (Atmospheric Pressure
- 20 Chemical Ionization). Desired products are seen as (M+ 1).

Compound	UV (220 nm) A%	ELSD A%	Mass Spec	Retention Time (Min)
132	57	67	607	10.14
133	48	54	621	10.35/10.78
134	62	77	573	10.15
135	59	72	523	9.54
136	29	33	675	11.47
137	37	33	573	10.21
138	47	48	613	11.07
139	30	33	635	10.81

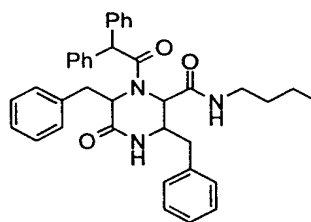
117



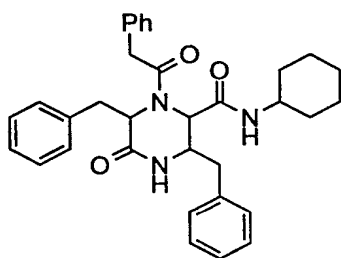
132



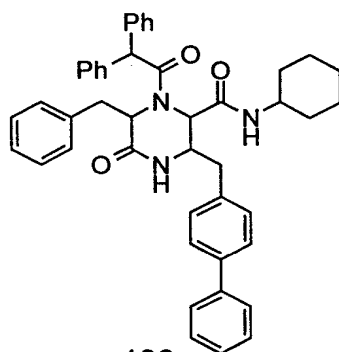
133



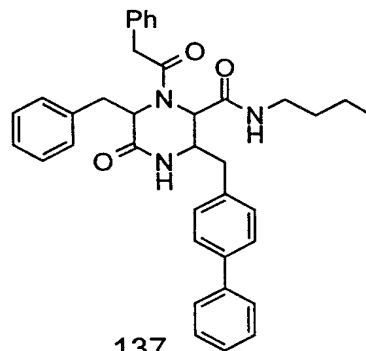
134



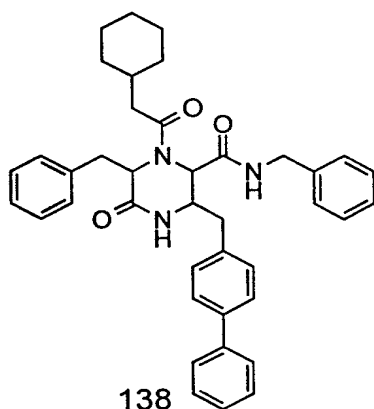
135



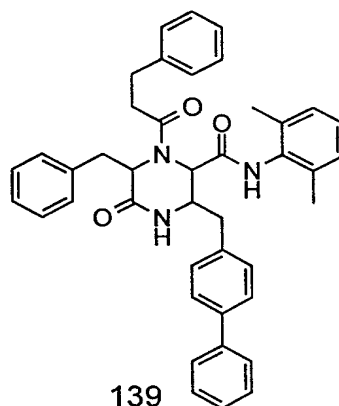
136



137



138

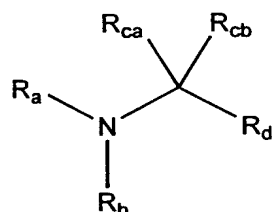


139

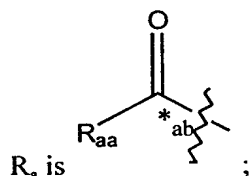
The present invention may be embodied in other specific forms without departing from the spirit
5 or essential attributes thereof.

WHAT IS CLAIMED IS:

1. A method for preparing a N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound of the formula



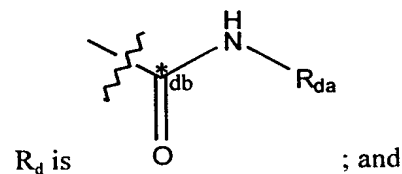
wherein



R_{aa} is hydrogen, optionally substituted aliphatic or optionally substituted aromatic;

R_b is hydrogen, optionally substituted aliphatic or optionally substituted aromatic;

R_{ca} and R_{cb} are independently hydrogen, optionally substituted aliphatic or optionally substituted aromatic;



R_{da} is optionally substituted aliphatic or optionally substituted aromatic; and

R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or at least one of R_b, R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

119

R_b is substituted with a primary or secondary protected amine that upon deprotection can react with the $*ab$ or $*db$ carbon, or at least one of R_{aa} , R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

- 5 R_{ca} and R_{cb} are independently substituted with a primary or secondary protected amine that upon deprotection can react with the $*ab$ or $*db$ carbon, or at least one of R_{aa} , R_b , R_{ca} , R_{cb} or R_{da} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring; or

- 10 R_{da} is substituted with a primary or secondary protected amine that upon deprotection can react with at least one of R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring,

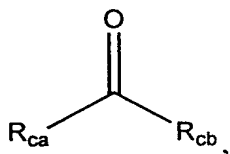
- 15 provided that when R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with R_b at least substituted with an activated carboxylic acid, then R_{aa} is other than substituted aliphatic,

comprising

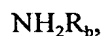
reacting the following four compounds:

20

an carbonyl compound of formula



- 25 an amine compound of formula



an isonitrile compound of formula

30



an acid compound of formula

- 35 $R_aCO_2H,$

to produce the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound.

2. The method according to claim 1 wherein

- 5 R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with the *db carbon, or at least one of R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring.

3. The method according to claim 1 wherein

- 10 R_{aa} is substituted with a primary or secondary protected amine that upon deprotection can react with R_b substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring.

4. The method according to claim 1 wherein

- 15 R_b is substituted with a primary or secondary protected amine that upon deprotection can react with the *db carbon, or at least one of R_{ca} or R_{cb} where each is at least substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring.

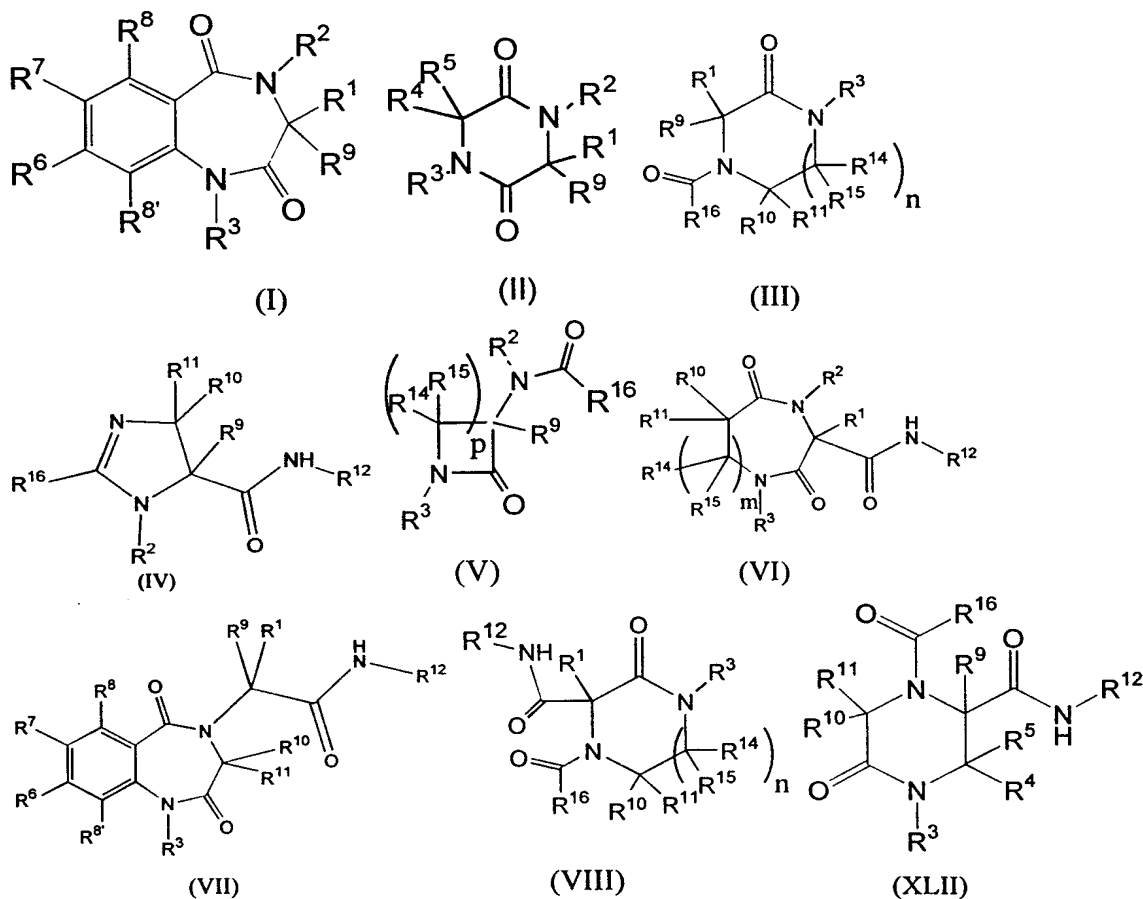
5. The method according to claim 1 wherein

- 20 R_{ca} and R_{cb} are independently substituted with a primary or secondary protected amine that upon deprotection can react with the *ab or *db carbon, or R_b , substituted with an activated carboxylic acid to form a 5-7 membered cyclic ring.

6. The method according to claim 1 further comprising deprotecting and cyclizing the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound to afford a cyclized compound selected from the group consisting of the following formulae:

25

(21)



5

wherein:

 $n = 1$ or 2 ; $m = 0$ or 1 ; $p = 2$;

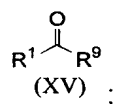
- 10 R¹ and R⁹ independently represent hydrogen, alkenyl, alkyl, aralkenyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl, or heterocyclyl;

15

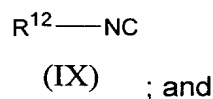
R² represents hydrogen, alkenyl, alkyl, aralkyl, aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, cycloalkyl, cycloalkenyl, heteroaralkyl, heteroaryl, fused heteroaryl cycloalkenyl, fused heteroaryl cycloalkyl, fused heteroaryl heterocyclenyl, fused heteroaryl heterocyclyl, heterocyclenyl or heterocyclyl;

20

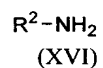
124



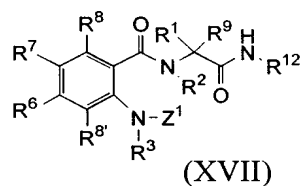
the isonitrile compound is of formula



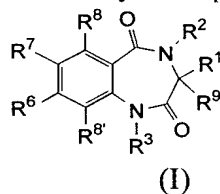
5 the amine compound is of formula



8. The method as claimed in claim 7 wherein the N-[(aliphatic or aromatic)carbonyl]-2-
10 aminoacetamide compound is of the formula

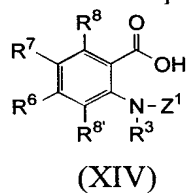


9. The method as claimed in claim 6 wherein cyclized product is



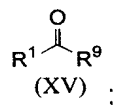
15

10. The method according to claim 1, wherein
the acid compound is of formula



wherein Z¹ is a suitable amine protecting group;

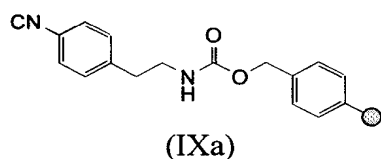
the carbonyl compound is of formula



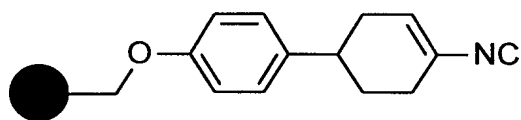
20

the isonitrile compound is selected from the group of formulae

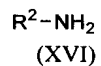
125



and

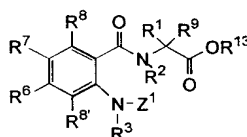


a solid support resin; and
the amine compound is of formula



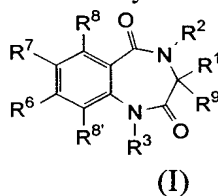
5

11. The method as claimed in claim 1 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula

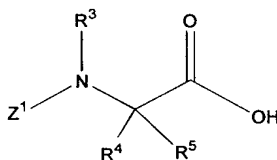


10

12. The method as claimed in claim 11 wherein cyclized product is

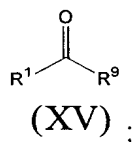


13. The method according to claim 1, wherein
the acid compound is of formula



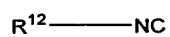
15

wherein Z^1 is a suitable amine protecting group;
the carbonyl compound is of formula



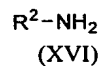
the isonitrile compound is selected from the group of formulae

(26)



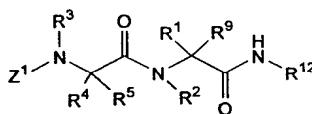
(IX) ;

and the amine compound is of formula



5

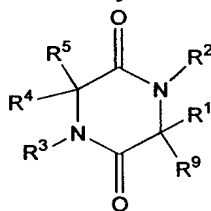
14. The method as claimed in claim 13 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



(XXIII)

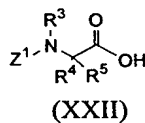
10

15. The method according to claim 14, wherein the cyclized compound is of the formula



(II)

15 16. The method according to claim 1, wherein the acid compound is of formula

wherein Z¹ is a suitable amine protecting group;

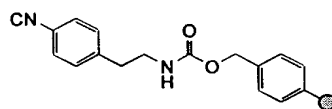
20

the carbonyl compound is of formula



the isonitrile compound is selected from the group of formula

127



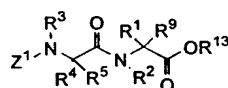
(IXa)

and the amine compound is of formula



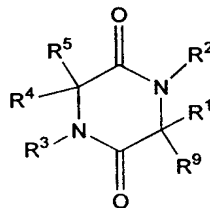
5

17. The method as claimed in claim 16 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



(XXV)

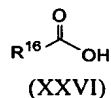
18. The method according to claim 17, wherein the cyclized compound is of the formula



(II)

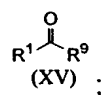
10

19. The method according to claim 1, wherein the acid compound is of formula

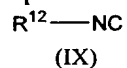


15

the carbonyl compound is of formula



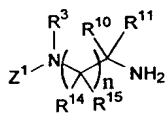
the isonitrile compound is selected from the group of formula



20

and the amine compound is of formula

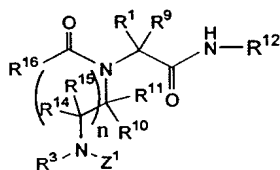
128



(XXVII) wherein Z¹ is a suitable amine protecting group.

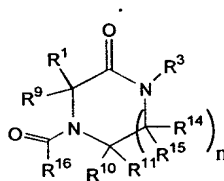
20. The method as claimed in claim 19 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula

5



(XXVIII)

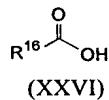
21. The method according to claim 20, wherein the cyclized compound is of the formula



(III)

10

22. The method according to claim 1, wherein the acid compound is of formula

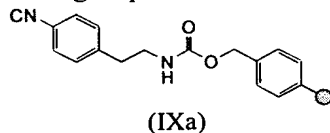


15

the carbonyl compound is of formula

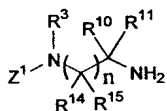


20 the isonitrile compound is selected from the group of formula



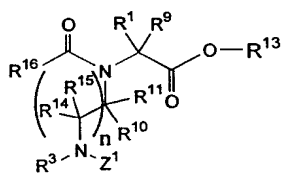
129

and the amine compound is of formula



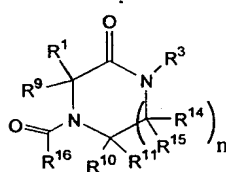
(XXVII) wherein Z¹ is a suitable amine protecting group.

- 5 23. The method as claimed in claim 22 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



(XXXI)

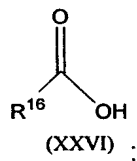
24. The method according to claim 23, wherein the cyclized compound is of the formula



(III)

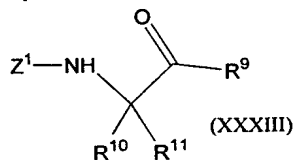
10

25. The method according to claim 1, wherein the acid compound is of formula



(XXVI) ;

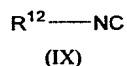
- 15 the carbonyl compound is of formula



(XXXIII)

wherein Z¹ is a suitable amine protecting group.;

the isonitrile compound is selected from the group of formula

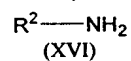


(IX)

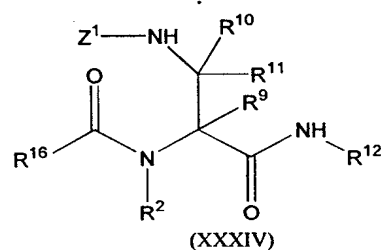
20

130

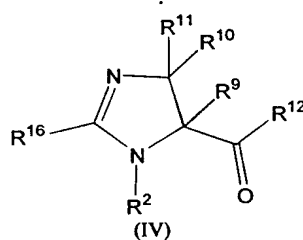
and the amine compound is of formula



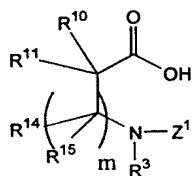
- 5 26. The method as claimed in claim 25 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



27. The method according to claim 26, wherein the cyclized compound is of the formula

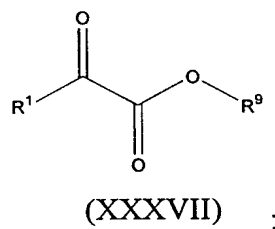


28. The method according to claim 1, wherein the acid compound is of formula



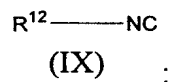
wherein Z¹ is a suitable amine protecting group;

the carbonyl compound is of formula

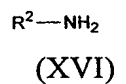


131

the isonitrile compound of formula

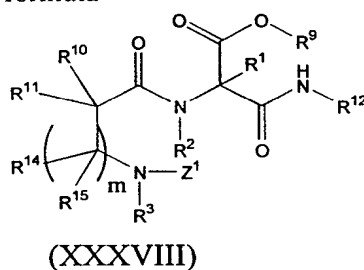


and the amine compound is of formula



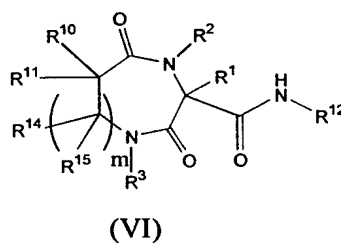
5

29. The method as claimed in claim 28 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



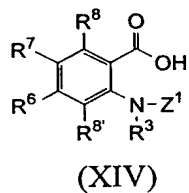
10

30. The method according to claim 29, wherein the cyclized compound is of the formula



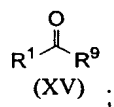
31. The method according to claim 1, wherein

15 the acid compound is of formula



wherein Z^1 is a suitable amine protecting group;

the carbonyl compound is of formula



the isonitrile compound is of formula

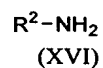
20

132



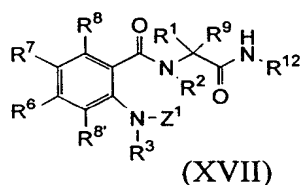
(IX) ; and

the amine compound is of formula

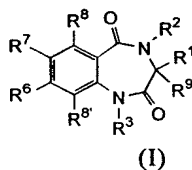


5

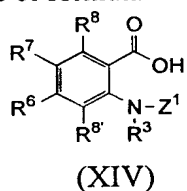
32. The method as claimed in claim 31 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



10 33. The method according to claim 32, wherein the cyclized compound is of the formula

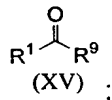


34. The method according to claim 1, wherein the acid compound is of formula

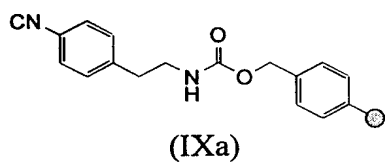


wherein Z¹ is a suitable amine protecting group;

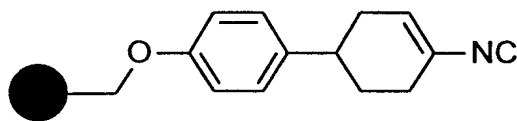
15 the carbonyl compound is of formula



the isonitrile compound is selected from the group of formulae



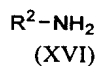
and



wherein  is a solid

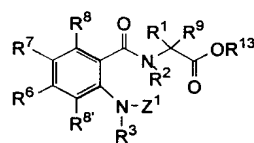
20 support resin; and the amine compound is of formula

133



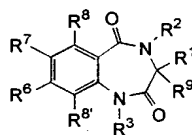
35. The method as claimed in claim 34 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula

5



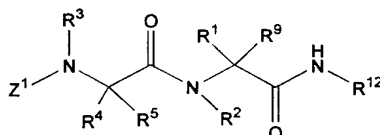
(XXI)

36. The method according to claim 35, wherein the cyclized compound is of the formula



(I)

10 37. The method according to claim 1, wherein the acid compound is of formula

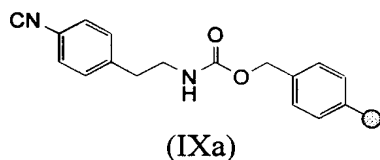


(XXIII)

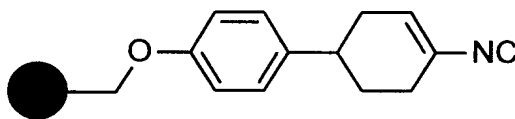
wherein Z¹ is a suitable amine protecting group;

the carbonyl compound is of formula;

15 the isonitrile compound is selected from the group of formulae



and

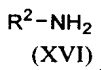


wherein  is a solid

support resin; and

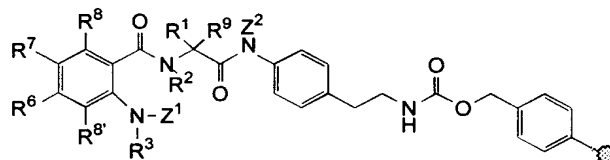
the amine compound is of formula

20



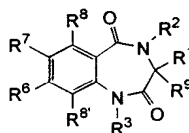
134

38. The method as claimed in claim 1 wherein the N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound is of the formula



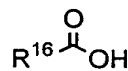
(XX)

39. The method according to claim 33, wherein the cyclized compound is of the formula



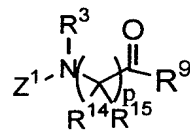
(I)

40. The method according to claim 1, wherein the acid compound is of formula



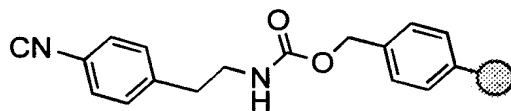
(XXVI) ;

the carbonyl compound is of formula



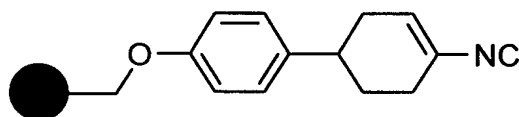
(XXXV) ;

the isonitrile compound is selected from the group consisting of formulae



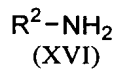
(IXa)

or



(XVIII); and

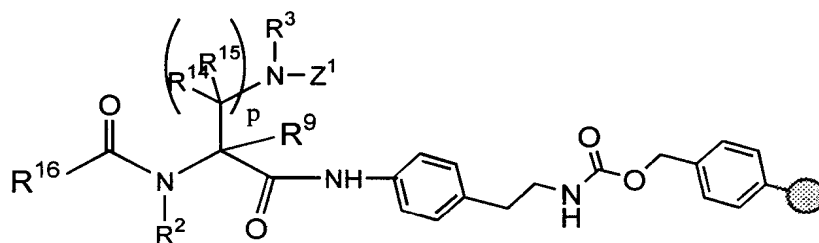
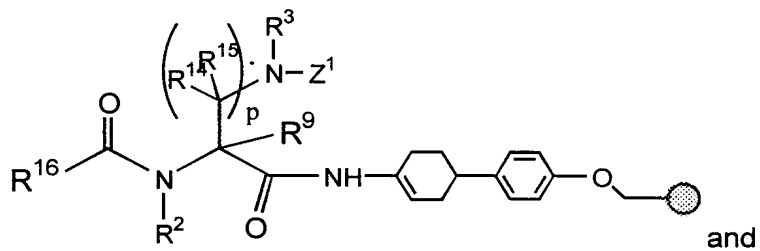
the amine compound is of formula



(XVI)

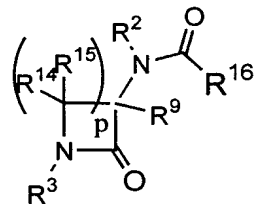
41. The method as claimed in claim 39 wherein the N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound is selected from the group of formulae

135



5

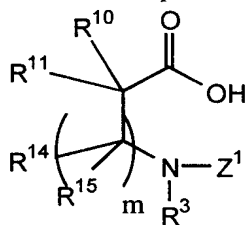
42. The method as claimed in claim 41 wherein cyclized product is



(V)

43. The method according to claim 1, wherein
the acid compound is of formula

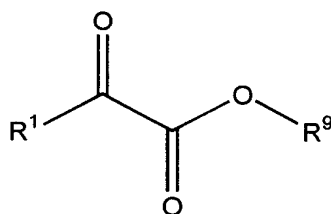
10



(XIV)

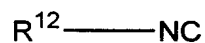
the carbonyl compound is of formula

136



(XXXVII)

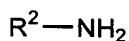
the isonitrile compound is of formula



(IX)

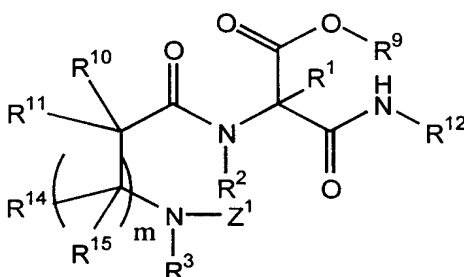
; and

5 the amine compound is of formula



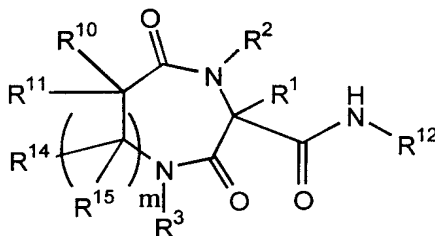
(XVI)

44. The method as claimed in claim 43 wherein the N-[(aliphatic or aromatic)carbonyl]-2-
10 aminoacetamide compound is of the formula



(XXXVIII)

45. The method as claimed in claim 44 wherein cyclized product is

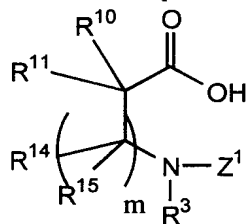


(VI)

46. The method according to claim 1, wherein

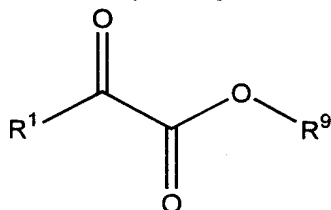
137

the acid compound is of formula



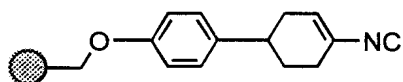
(XIV)

the carbonyl compound is of formula



(XXXVII)

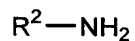
5 the isonitrile compound is of formula



(XVIII)

; and

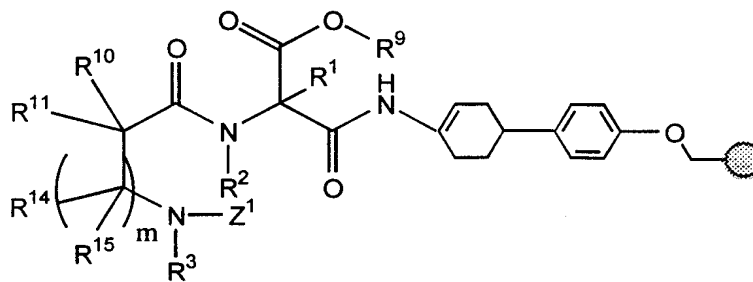
the amine compound is of formula



(XVI)

10

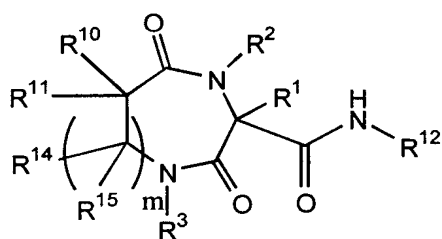
47. The method as claimed in claim 46 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula



15

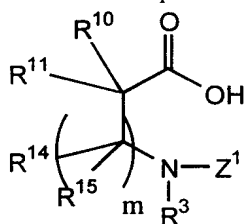
48. The method as claimed in claim 47 wherein cyclized product is

138



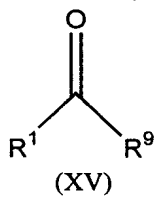
(VI)

49. The method according to claim 1, wherein the acid compound is of formula



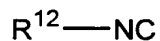
(XIV)

the carbonyl compound is of formula



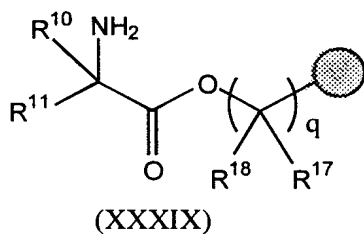
(XV)

the isonitrile compound is of formula



(IX)

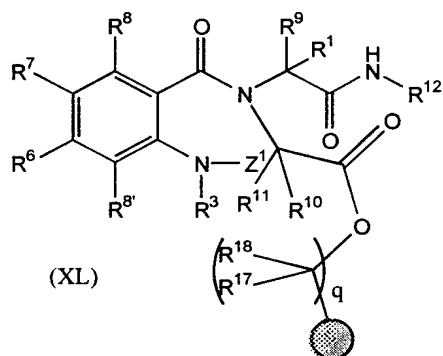
the amine compound is of formula



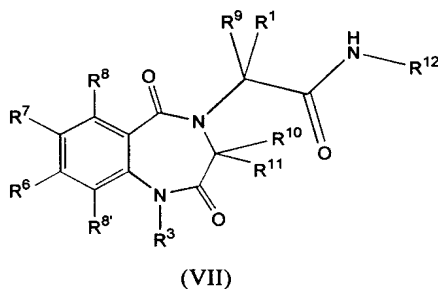
(XXXIX)

50. The method as claimed in claim 49 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula

139

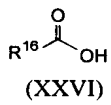


51. The method as claimed in claim 50 wherein cyclized product is

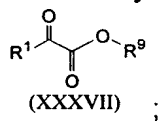


5

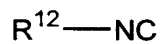
52. The method according to claim 1, wherein the acid compound is of formula



10 the carbonyl compound is of formula

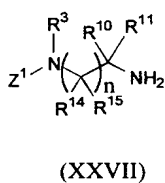


the isonitrile compound is of formula



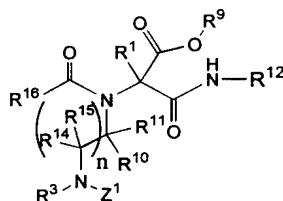
(IX) ; and

15 the amine compound is of formula



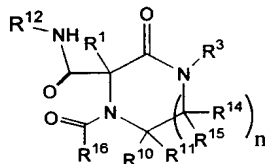
140

53. The method as claimed in claim 52 wherein the N-[(aliphatic or aromatic)carbonyl)]-2-aminoacetamide compound is of the formula



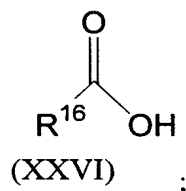
(XLI)

54. The method as claimed in claim 53 wherein cyclized product is



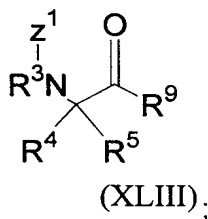
(VIII)

10 55. The method according to claim 1, wherein the acid compound is of formula



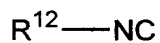
(XXVI) ;

the carbonyl compound is of formula



(XLIII);

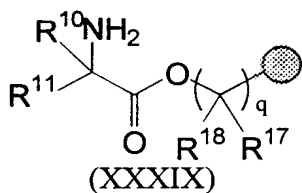
15 the isonitrile compound is of formula



(IX) ; and

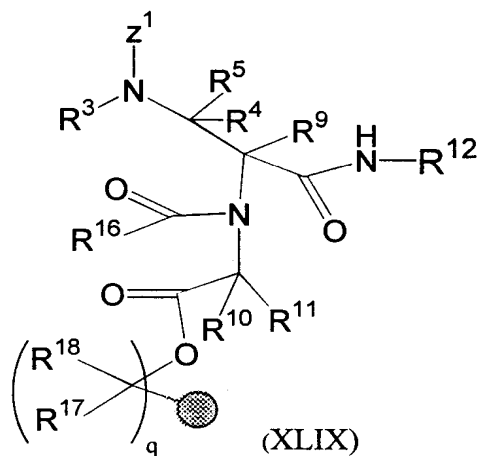
the amine compound is of formula

141

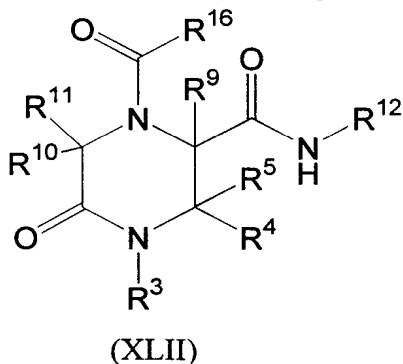


56. The method as claimed in claim 55 wherein the N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compound is of the formula

5



57. The method as claimed in claim 56 wherein cyclized product is



10

58. The method according to claim 6 wherein the cyclized product comprises a compound wherein

$n = 1$.

15 59. The method according to claim 6 wherein the cyclized product comprises a compound wherein

$n = 2$.

142

60. The method according to claim 6 wherein the cyclized product comprises a compound wherein
m = 0.

5

61. The method according to claim 6 wherein the cyclized product comprises a compound wherein
m = 1.

10 62. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R⁹ is hydrogen.

15 63. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R⁹ is alkyl.

20 64. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R¹ is aralkyl, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

25 65. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R² represents aralkyl, alkyl, fused arylheterocyclenyl, or fused arylheterocyclyl.

30 66. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R³ represents hydrogen, alkyl, aralkyl, cycloalkyl, cycloalkenyl, heteroaralkyl or heterocyclenyl,
heterocyclyl.

67. The method according to claim 6 wherein the cyclized product comprises a compound wherein R³ represents hydrogen.

35 68. The method according to claim 6 wherein the cyclized product comprises a compound wherein
R⁴ and R⁵ independently represents alkyl, aralkyl, heteroaralkyl, heterocyclyl, or cycloalkyl.

69. The method according to claim 6 wherein the cyclized product comprises a

143

compound wherein

R⁶, R⁷, R⁸ and R^{8'}, independently represents hydrogen, halo, alkoxy, alkyl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, fused heteroarylcyloalkenyl, fused heteroarylcyloalkyl, fused heteroarylheterocyclenyl, fused heteroarylheterocyclyl, or heteroaryl.

5

70. The method according to claim 6 wherein the cyclized product comprises a compound wherein

R¹⁰, R¹¹, R¹⁴ and R¹⁵ independently represent hydrogen, alkyl, or aralkyl.

10

71. The method according to claim 6 wherein the cyclized product comprises a compound wherein

R¹² represents alkyl, aralkyl, aryl, cycloalkyl, or heterocyclyl.

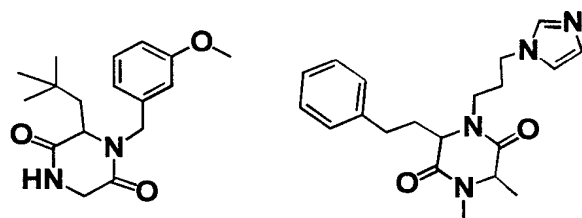
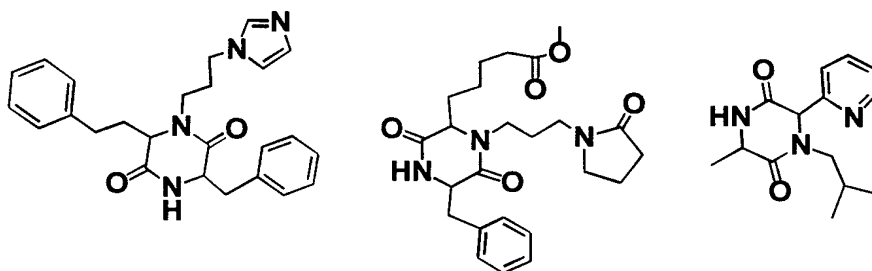
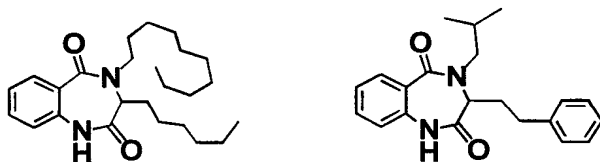
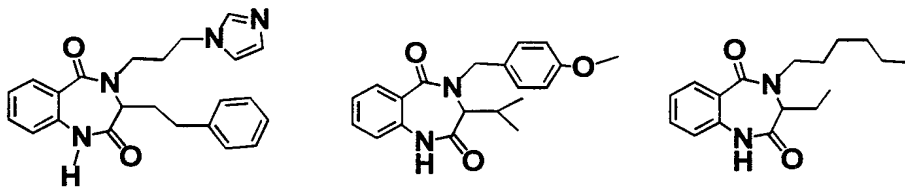
15

72. The method according to claim 6 wherein the cyclized product comprises a compound wherein

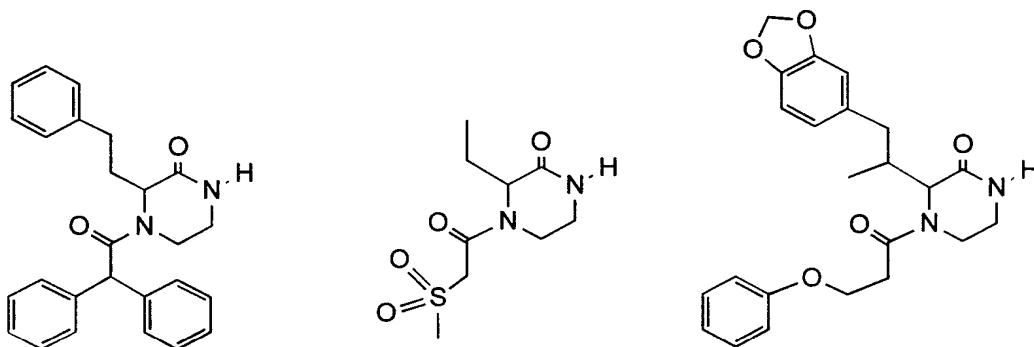
R¹⁶ represents alkyl, fused arylheterocyclyl, aralkyl, cycloalkyl, heteroaryl, aryl, heteroaralkyl, alkenyl, heteroaralkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused heteroarylcyloalkenyl, fused heteroarylheterocyclyl, heterocyclenyl or heterocyclyl.

144

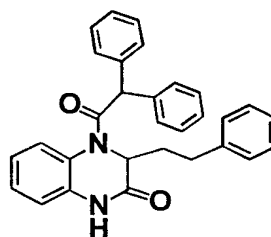
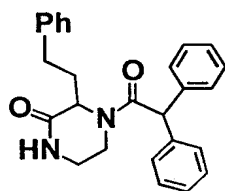
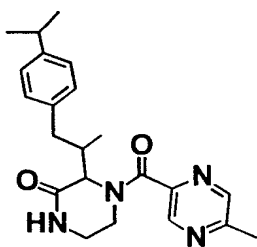
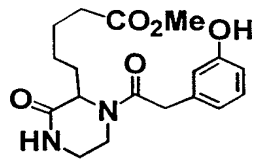
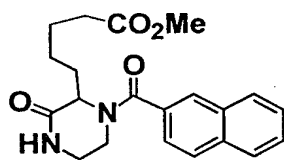
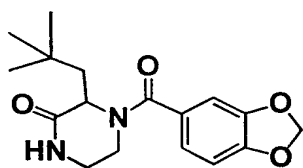
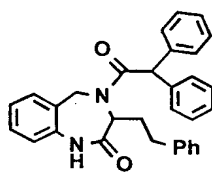
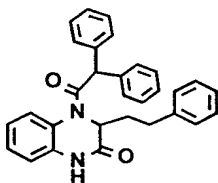
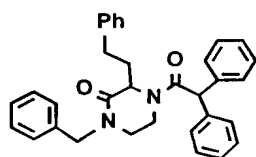
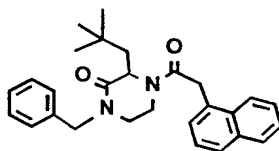
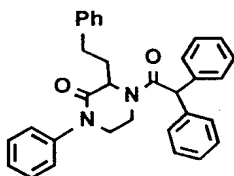
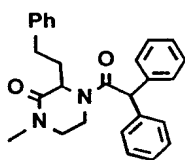
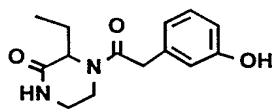
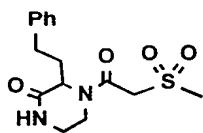
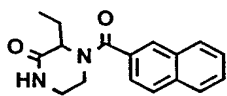
73. The method according to claim 6 wherein the cyclized product is selected from the group of formulae consisting of:



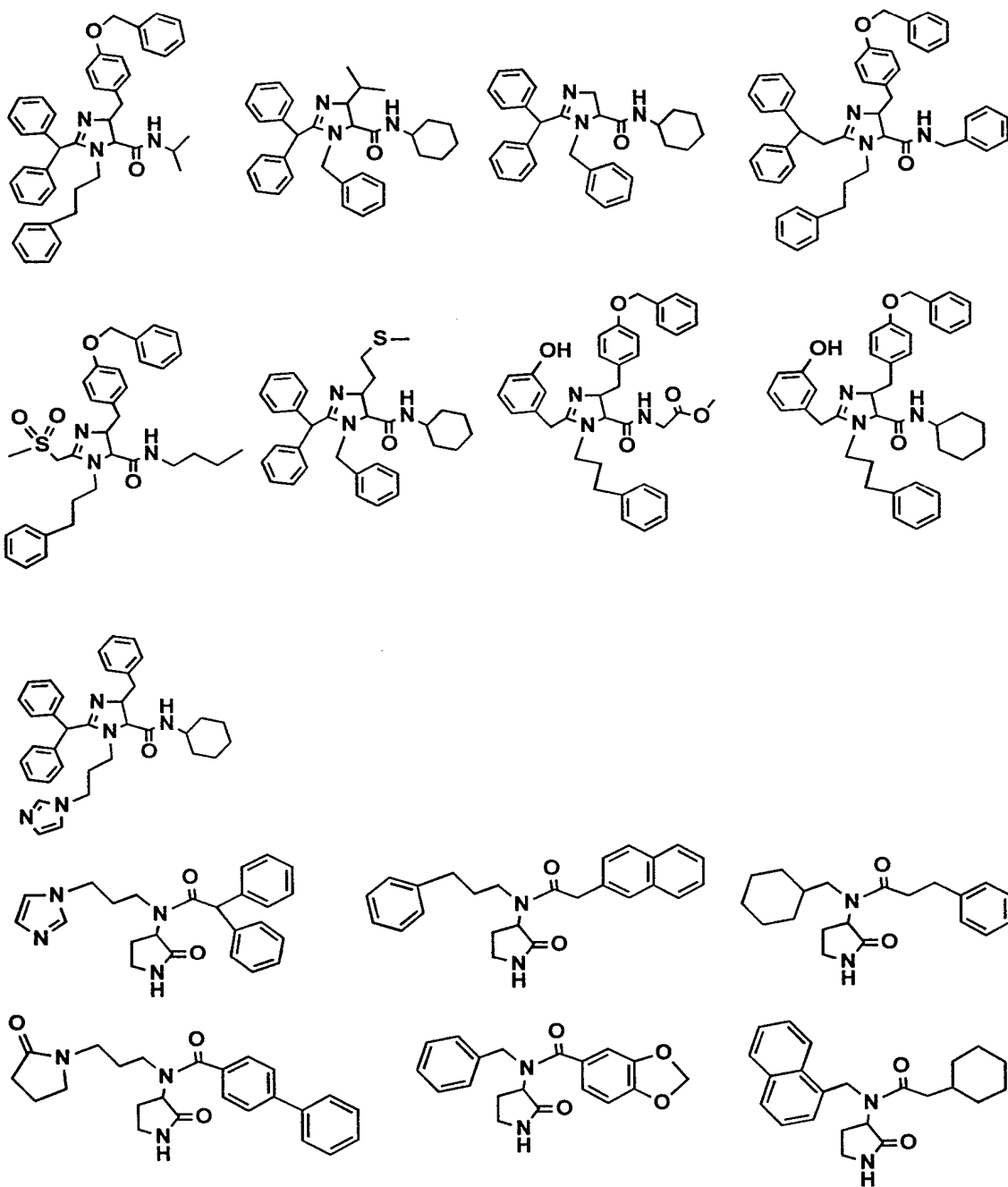
5



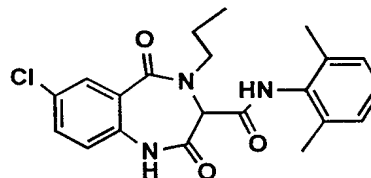
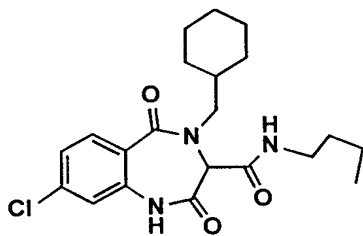
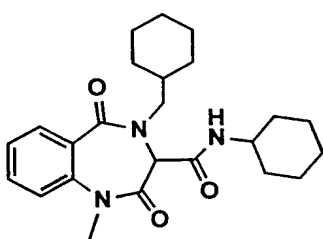
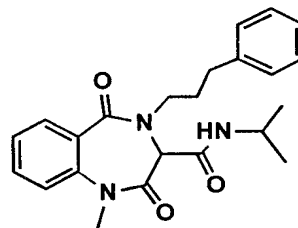
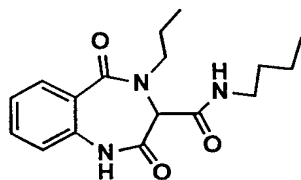
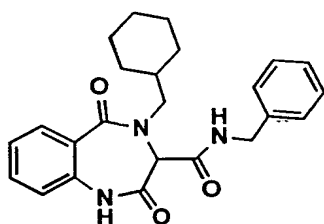
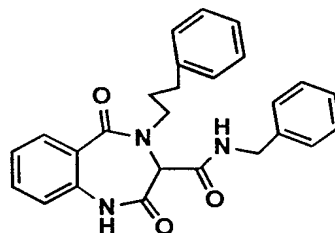
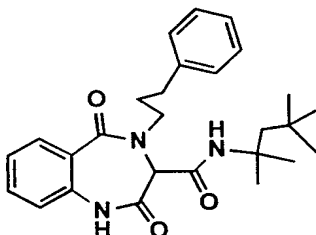
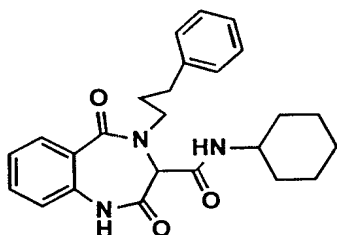
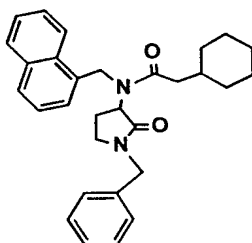
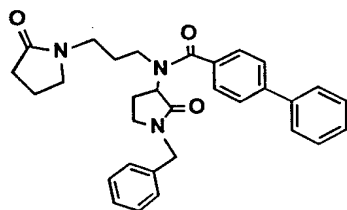
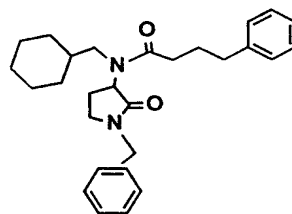
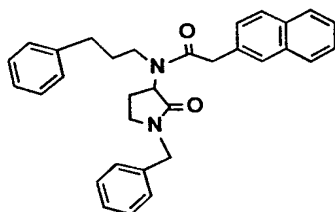
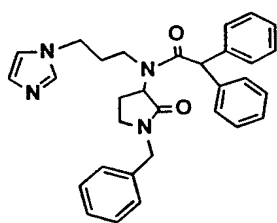
145



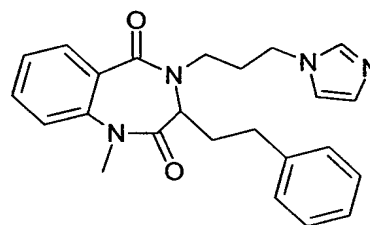
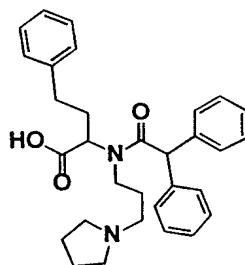
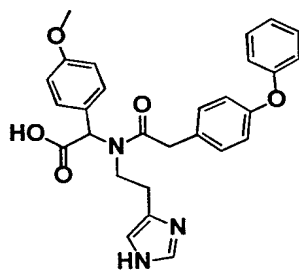
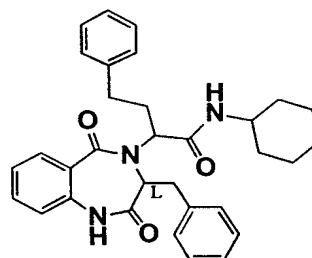
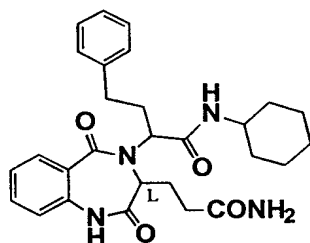
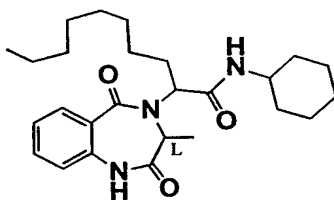
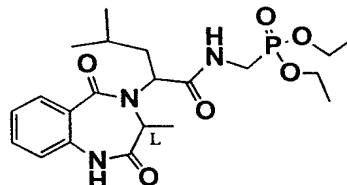
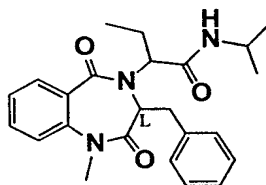
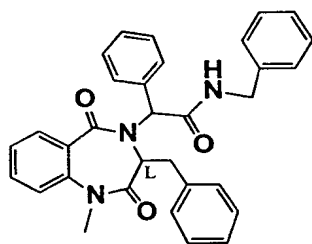
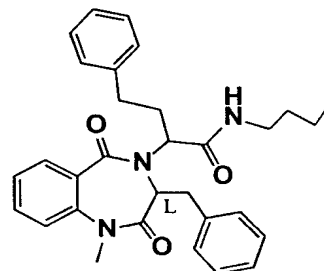
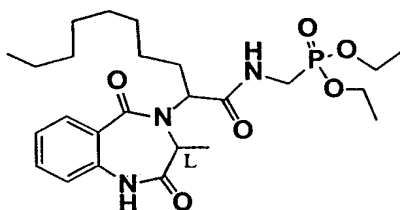
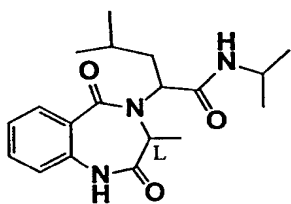
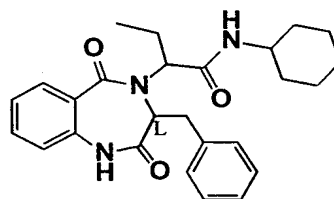
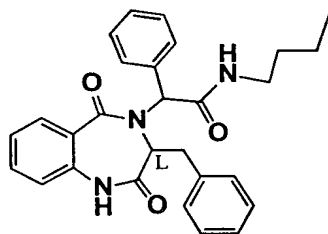
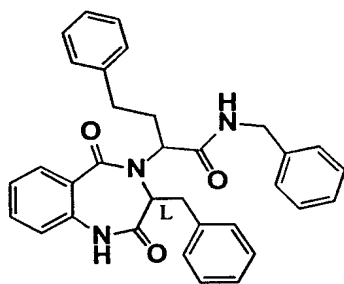
46



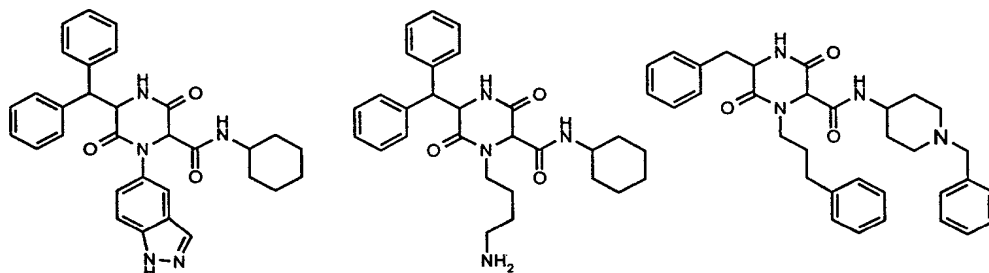
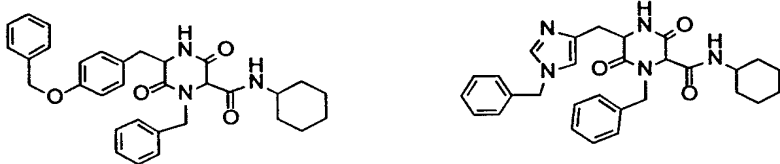
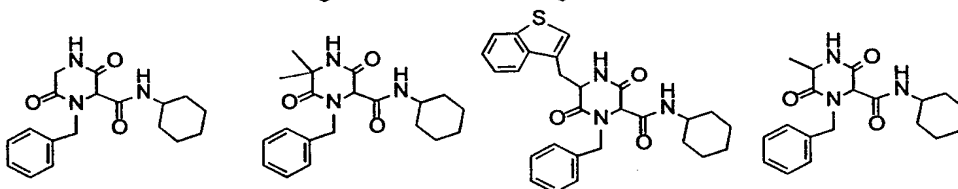
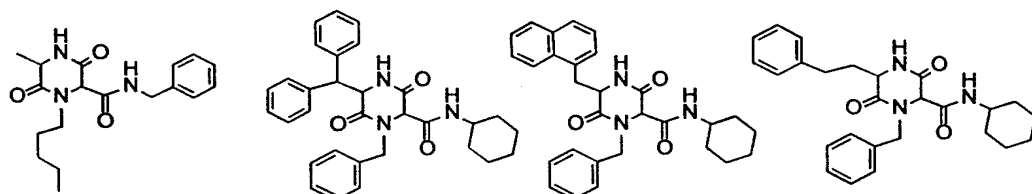
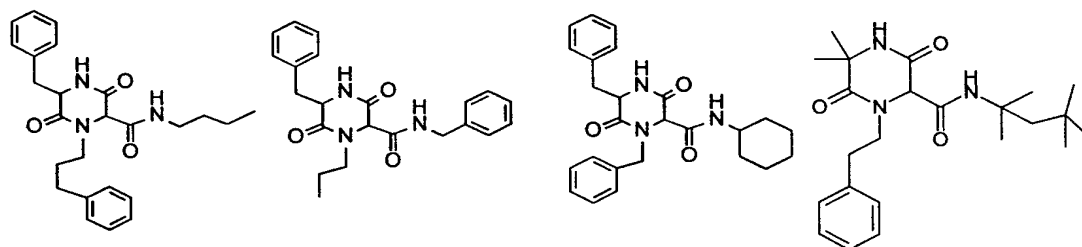
147



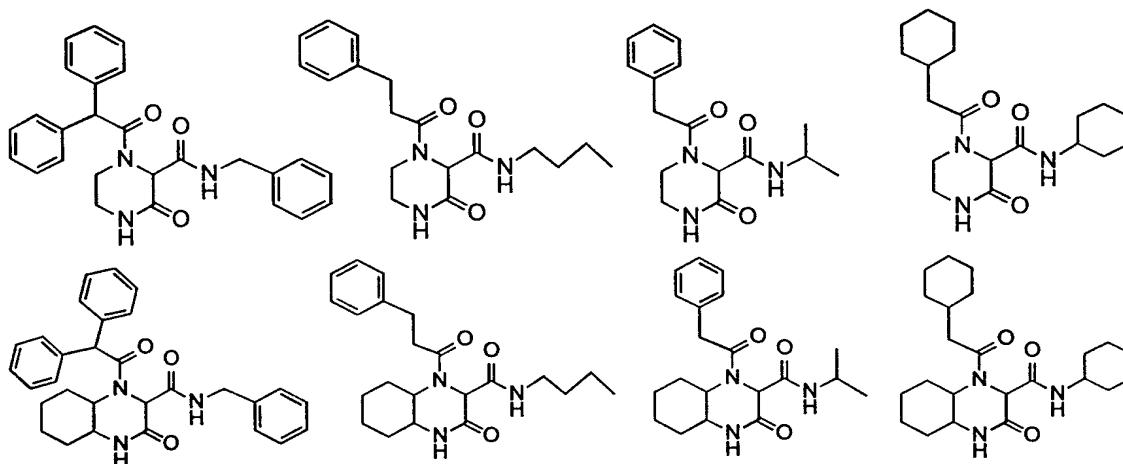
148



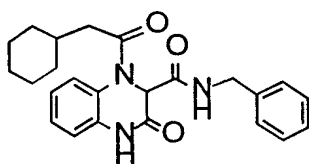
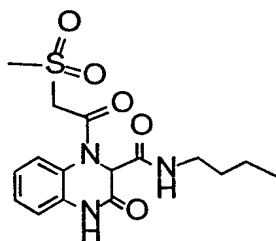
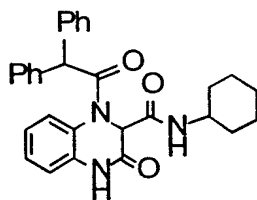
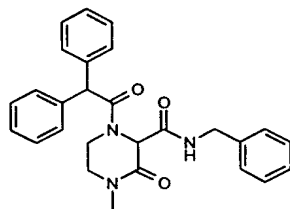
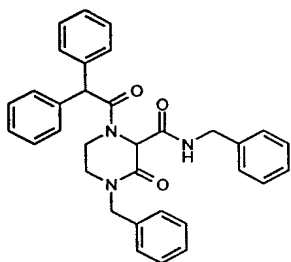
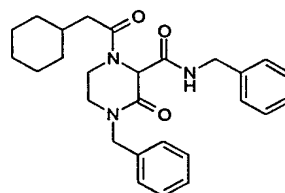
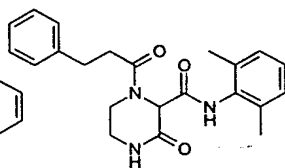
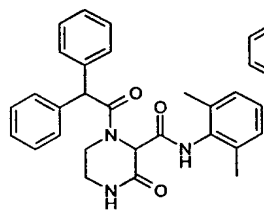
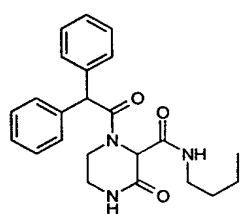
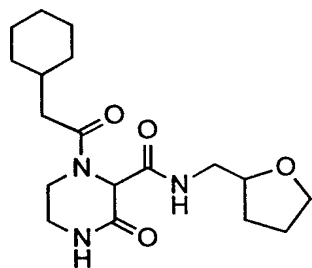
144



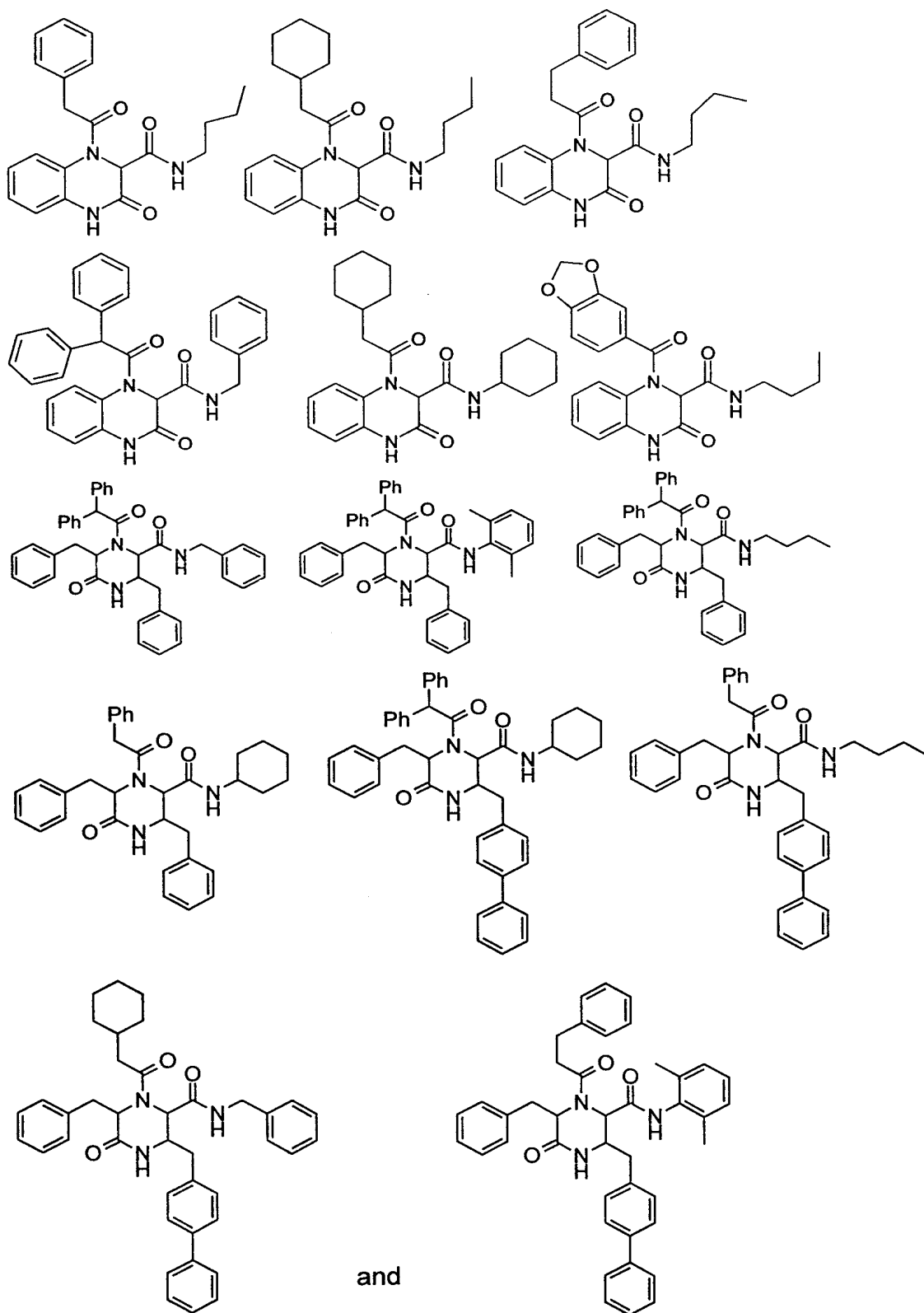
5



150

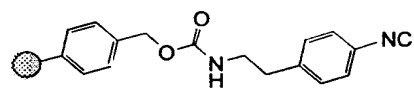


151




152

68. A resin bound isonitrile of formula



(IXa)

wherein  is a solid support resin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/01923

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/200, 362, 504, 506, 507; 544/354, 355, 359, 360, 370, 374, 377; 560/27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FUKUYAMA et al. Synthetic Approach to Bicyclomycin: Synthesis of the Bicyclic System of Bicyclomycin. Tetrahedron Letters. 1981, Vol. 22, No. 42, pages 4155-4158, especially page 4156.	1-68
Y	FAILLI et al. Model Experiments Directed towards the Synthesis of N-aminopeptides. Canadian Journal of Chemistry. 1973, Vol. 51, pages 2769-2775, especially see page 2771.	1-68
Y	BOEHM et al. Rapid and Convenient Synthesis of Polyoxin Containing N-Methylated Peptide Bonds. Journal of Organic Chemistry. 1986, Vol. 51, pages 2307-2314, especially see page 2308, col 2.	1-68



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* & * document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 MAY 1999

Date of mailing of the international search report

25 MAY 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SHAIENDRA KUMAR

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/01923

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07D 205/00, 205/08, 243/12, 243/24, 241/04, 241/36, 231/00, 233/22, 207/00, 207/12, 401/00, 403/00, 405/00; C07C 261/02

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

540/200, 362, 504, 506, 507; 544/354, 355, 359, 360, 370, 374, 377; 560/27